09/980464

```
=> d his

     (FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1       1280537 S KINASE?
L2        385991 S LYMPH(A)NODE?
L3         65436 S STROMAL(W)CELL
L4          5129 S L1 AND L2
L5            92 S L3 AND L4
L6            50 DUP REM L5 (42 DUPLICATES REMOVED)
L7             0 S L3(W)L2(W)L1
L8            15 S L1(2W)L2
L9            13 DUP REM L8 (2 DUPLICATES REMOVED)
L10      6902623 S CLON? OR EXPRESS? OR RECOMBINANT
L11           50 S (L6 OR L9) AND L10
L12      3908319 S MURINE OR MOUSE
L13          176 S MLKS##
L14           31 S L12 AND L13
L15           11 DUP REM L14 (20 DUPLICATES REMOVED)
L16           24 S L6 AND L12
L17           24 DUP REM L16 (0 DUPLICATES REMOVED)
L18            0 S L13 AND "MLKS-2"
                 E BIRD T A/AU
L19          197 S E3
                 E VIRCA G D/AU
L20          180 S E3-E6
                 E MARTIN U/AU
L21          752 S E3
                 E ANDERSON D M/AU
L22         1925 S E3
L23         3018 S L19 OR L20 OR L21 OR L22
L24            0 S L13 AND L23
L25            1 S L4 AND L23

=>
```

```
Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1652MXM

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 01  New pricing for the Save Answers for SciFinder Wizard within
                  STN Express with Discover!
 NEWS  4  OCT 28  KOREAPAT now available on STN
 NEWS  5  NOV 30  PHAR reloaded with additional data
 NEWS  6  DEC 01  LISA now available on STN
 NEWS  7  DEC 09  12 databases to be removed from STN on December 31, 2004
 NEWS  8  DEC 15  MEDLINE update schedule for December 2004
 NEWS  9  DEC 17  ELCOM reloaded; updating to resume; current-awareness
                  alerts (SDIs) affected
 NEWS  10 DEC 17  COMPUAB reloaded; updating to resume; current-awareness
                  alerts (SDIs) affected
 NEWS  11 DEC 17  SOLIDSTATE reloaded; updating to resume; current-awareness
                  alerts (SDIs) affected
 NEWS  12 DEC 17  CERAB reloaded; updating to resume; current-awareness
                  alerts (SDIs) affected
 NEWS  13 DEC 17  THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
 NEWS  14 DEC 30  EPFULL: New patent full text database to be available on STN
 NEWS  15 DEC 30  CAPLUS - PATENT COVERAGE EXPANDED
 NEWS  16 JAN 03  No connect-hour charges in EPFULL during January and
                  February 2005
 NEWS  17 JAN 26  CA/CAPLUS - Expanded patent coverage to include the Russian
                  Agency for Patents and Trademarks (ROSPATENT)

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005
```

```
=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.68       1.68

FILE 'MEDLINE' ENTERED AT 14:04:41 ON 03 FEB 2005

FILE 'EMBASE' ENTERED AT 14:04:41 ON 03 FEB 2005
COPYRIGHT (C) 2005 Elsevier Inc. All rights reserved.

FILE 'BIOSIS' ENTERED AT 14:04:41 ON 03 FEB 2005
Copyright (c) 2005 The Thomson Corporation.

FILE 'BIOTECHDS' ENTERED AT 14:04:41 ON 03 FEB 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE 'SCISEARCH' ENTERED AT 14:04:41 ON 03 FEB 2005
Copyright (c) 2005 The Thomson Corporation.

FILE 'HCAPLUS' ENTERED AT 14:04:41 ON 03 FEB 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'NTIS' ENTERED AT 14:04:41 ON 03 FEB 2005
Compiled and distributed by the NTIS, U.S. Department of Commerce.
It contains copyrighted material.
All rights reserved. (2005)

FILE 'LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
COPYRIGHT (C) 2005 Cambridge Scientific Abstracts (CSA)


=> s kinase?
L1     1280537 KINASE?

=> s lymph(a)node?
L2      385991 LYMPH(A) NODE?

=> s stromal(w)cell
<------User Break------>

SEARCH ENDED BY USER
SEARCH ENDED BY USER

=> s stromal(w)cell
   4 FILES SEARCHED...
L3       65436 STROMAL(W) CELL

=> s l1 and l2
L4        5129 L1 AND L2

=> s l3 and l4
L5          92 L3 AND L4

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6           50 DUP REM L5 (42 DUPLICATES REMOVED)

=> d 1-50 ibib ab

L6   ANSWER 1 OF 50  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:371064  HCAPLUS
DOCUMENT NUMBER:          140:373461
```

TITLE: Evaluation of breast cancer states and outcomes using gene expression profiles

INVENTOR(S): West, Mike; Nevins, Joseph R.; Huang, Andrew

PATENT ASSIGNEE(S): Synpac, Inc., USA; Duke Univerisity

SOURCE: PCT Int. Appl., 799 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037996	A2	20040506	WO 2003-US33656	20031024
WO 2004037996	A3	20041229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004083084	A1	20040429	US 2002-291878	20021112
WO 2004044839	A2	20040527	WO 2002-US38216	20021112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004106113	A1	20040603	US 2002-291886	20021112

PRIORITY APPLN. INFO.:

US 2002-420729P	P	20021024
US 2002-421062P	P	20021025
US 2002-421102P	P	20021025
US 2002-424701P	P	20021108
US 2002-424715P	P	20021108
US 2002-424718P	P	20021108
US 2002-291878	A	20021112
US 2002-291886	A	20021112
US 2002-425256P	P	20021112
WO 2002-US38216	A	20021112
WO 2002-US38222	A	20021112
US 2003-448461P	P	20030221
US 2003-448462P	P	20030221
US 2003-457877P	P	20030327
US 2003-458373P	P	20030331

AB The present invention relates generally to a method for evaluating and/or predicting breast cancer states and outcomes by measuring gene and metagene expression levels and integrating such data with clin. risk factors. Genes and metagenes whose expressions are correlated with a particular breast cancer risk factor or phenotype are provided using binary prediction tree modeling. The invention provides 175 genes associated with metagene predictors of **lymph node** metastasis, 216 genes associated with metagene predictors of breast cancer recurrence, and 496 metagenes related to breast cancer study. Methods of using the subject genes and metagenes in diagnosis and treatment methods, as well as drug screening methods, etc are also provided. In addition, reagents, media

and kits that find use in practicing the subject methods are also provided.

L6 ANSWER 2 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:308529 HCAPLUS
DOCUMENT NUMBER: 140:333599
TITLE: Gene expression profile of human and mouse genes in atopic dermatitis and psoriasis patients and its use for diagnosis, therapy, and drug screening
INVENTOR(S): Itoh, Mikito; Ogawa, Kaoru; Shinagawa, Akira; Sudo, Hajime; Ogawa, Hideoki; Ra, Chisei; Mitsuishi, Kouichi
PATENT ASSIGNEE(S): Genox Research, Inc., Japan; Juntendo University
SOURCE: PCT Int. Appl., 611 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004031386	A1	20040415	WO 2003-JP9808	20030801

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2002-229318 A 20020806
JP 2003-136543 A 20030514

AB This invention provides gene expression profile between a rash site and a no-rash site in a patient with atopic dermatitis or a patient with psoriasis. The invention also provides gene expression profile between a no-rash site in such a disease and a normal subject. Animal models, particularly mouse for those diseases are also claimed. The gene expression profile provided in this invention can be used for diagnosis, therapy, and drug screening for atopic dermatitis and psoriasis.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 50 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004627248 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15585839
TITLE: Intestinal cryptopatch formation in mice requires lymphotoxin alpha and the lymphotoxin beta receptor.
AUTHOR: Taylor Rebekah T; Lugering Andreas; Newell Kenneth A; Williams Ifor R
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA.
CONTRACT NUMBER: DK64399 (NIDDK)
DK64730 (NIDDK)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Dec 15) 173 (12) 7183-9.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20041220

Last Updated on STN: 20041220

AB Interactions between lymphotoxin (LT)alpha(1)beta(2) on inducer cells and the lymphotoxin beta receptor (LTbetaR) on **stromal cells** initiate development of **lymph nodes** and Peyer's patches. In this study, we assessed the contributions of LTalpha and LTbetaR to the development of cryptopatches (CP), aggregates of T cell precursors in the mouse small intestine. Mice genetically deficient in LTalpha or LTbetaR lacked CP. Bone marrow from LTalpha-deficient mice was unable to initiate development of CP or isolated lymphoid follicles (ILF) after transfer to CD132-null mice lacking CP and ILF. However, LTalpha-deficient bone marrow-derived cells contributed to CP formed in CD132-null mice receiving a mixture of wild-type and LTalpha-deficient bone marrow cells. Transfer of wild-type bone marrow into irradiated LTalpha-deficient mice resulted in reconstitution of both CP and ILF. However, the LT-dependent formation of CP was distinguished from the LT-dependent formation of ILF and Peyer's patches by not requiring the presence of an intact NF-kappaB-inducing **kinase** gene. CP but not ILF were present in the small intestine from NF-kappaB-inducing **kinase**-deficient alymphoplasia mice, indicating that the alternate NF-kappaB activation pathway required for other types of LTbetaR-dependent lymphoid organogenesis is dispensable for CP development. In addition, we identified VCAM-1(+) cells within both CP and ILF that are candidates for the **stromal cells** involved in receiving LT-dependent signals from the hemopoietic precursors recruited to CP. These findings demonstrate that interactions between cells expressing LTalpha(1)beta(2) and LTbetaR are a shared feature in the development of all small intestinal lymphoid aggregates.

L6 ANSWER 4 OF 50 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004572999 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15492752
TITLE: Acquisition of **lymph node**, but not distant metastatic potentials, by the overexpression of CXCR4 in human oral squamous cell carcinoma.
AUTHOR: Uchida Daisuke; Begum Nasima-Mila; Tomizuka Yoshifumi; Bando Takashi; Almofti Ammar; Yoshida Hideo; Sato Mitsunobu
CORPORATE SOURCE: Second Department of Oral and Maxillofacial Surgery, Tokushima University School of Dentistry, Kuramoto, Tokushima, Japan.. daisuke@dent.tokushima-u.ac.jp
SOURCE: Laboratory investigation; a journal of technical methods and pathology, (2004 Dec) 84 (12) 1538-46. Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041117
Last Updated on STN: 20041220

AB Recently, it has been suggested that chemokine/receptor interactions determine the destination of the invasive tumor cells in several types of cancer. It has also been proposed that the **stromal cell** -derived factor-1 (SDF-1; CXCL12)/CXCR4 system might be involved **lymph node** metastasis in oral squamous cell carcinoma (SCC). In order to further clarify the role of the SDF-1/CXCR4 system in oral SCC, we generated CXCR4 stable transfectants (IH-CXCR4) using oral SCC cells, and compared them to IH, which did not express CXCR4 and which did not have **lymph node** metastatic potentials in vivo. We introduced enhanced green fluorescent protein (GFP) fused-CXCR4 into IH cells, and detected the GFP fluorescence in the cytoplasm and cell membrane in approximately 60% of the G418-resistant cells. This bulk-transfectant expressed a high level of CXCR4 mRNA and protein, and exhibited the characteristic calcium fluxes and chemotactic activity observed in treatment with SDF-1. SDF-1 biphasically activated extracellular signal-regulated **kinase** (ERK)1/2, but continuously

activated Akt/protein **kinase** B (PKB) in IH-CXCR4 cells. Most importantly, IH-CXCR4 cells frequently metastasized to the cervical **lymph node**, but not to the distant organs in the orthotopic inoculation of nude mice. Furthermore, these **lymph node** metastases were inhibited by the treatment of a mitogen-activated protein **kinase**/ERK **kinase** inhibitor, U0126, or a phosphatidylinositol 3 **kinase** inhibitor, wortmannin. These results indicate that SDF-1/CXCR4 signaling mediates the establishment of **lymph node** metastasis in oral SCC via ERK1/2 or Akt/PKB pathway.

L6 ANSWER 5 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:954345 HCAPLUS
DOCUMENT NUMBER: 141:377496
TITLE: Ink4a/Arf expression is a biomarker of aging
AUTHOR(S): Krishnamurthy, Janakiraman; Torrice, Chad; Ramsey, Matthew R.; Kovalev, Grigoriy I.; Al-Regaiey, Khalid; Su, Lishan; Sharpless, Norman E.
CORPORATE SOURCE: Departments of Medicine and Genetics, The Lineberger Comprehensive Cancer Center, The University of North Carolina School of Medicine, Chapel Hill, NC, USA
SOURCE: Journal of Clinical Investigation (2004), 114(9), 1299-1307
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Ink4a/Arf locus encodes 2 tumor suppressor mols., p16INK4a and Arf, which are principal mediators of cellular senescence. To study the links between senescence and aging in vivo, we examined Ink4a/Arf expression in rodent models of aging. We show that expression of p16INK4a and Arf markedly increases in almost all rodent tissues with advancing age, while there is little or no change in the expression of other related cell cycle inhibitors. The increase in expression is restricted to well-defined compartments within each organ studied and occurs in both epithelial and **stromal cells** of diverse lineages. The age-associated increase in expression of p16INK4a and Arf is attenuated in the kidney, ovary, and heart by caloric restriction, and this decrease correlates with diminished expression of an in vivo marker of senescence, as well as decreased pathol. of those organs. Last, the age-related increase in Ink4a/Arf expression can be independently attributed to the expression of Ets-1, a known p16INK4a transcriptional activator, as well as unknown Ink4a/Arf coregulatory mols. These data suggest that expression of the Ink4a/Arf tumor suppressor locus is a robust biomarker, and possible effector, of mammalian aging.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2004286637 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15186750
TITLE: Requirement for Tec **kinases** in chemokine-induced migration and activation of Cdc42 and Rac.
AUTHOR: Takesono Aya; Horai Reiko; Mandai Michiko; Dombroski Derek; Schwartzberg Pamela L
CORPORATE SOURCE: National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: Current biology : CB, (2004 May 25) 14 (10) 917-22. Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407

ENTRY DATE: Entered STN: 20040610
Last Updated on STN: 20040721
Entered Medline: 20040720

AB Cell polarization and migration in response to chemokines is essential for proper development of the immune system and activation of immune responses. Recent studies of chemokine signaling have revealed a critical role for PI3-**Kinase**, which is required for polarized membrane association of pleckstrin homology (PH) domain-containing proteins and activation of Rho family GTPases that are essential for cell polarization and actin reorganization. Additional data argue that tyrosine **kinases** are also important for chemokine-induced Rac activation. However, how and which **kinases** participate in these pathways remain unclear. We demonstrate here that the Tec **kinases** Itk and Rlk play an important role in chemokine signaling in T lymphocytes. Chemokine stimulation induced transient membrane association of Itk and phosphorylation of both Itk and Rlk, and purified T cells from Rlk(-/-)Itk(-/-) mice exhibited defective migration to multiple chemokines in vitro and decreased homing to **lymph nodes** upon transfer to wt mice. Expression of a dominant-negative Itk impaired SDF-1alpha-induced migration, cell polarization, and activation of Rac and Cdc42. Thus, Tec **kinases** are critical components of signaling pathways required for actin polarization downstream from both antigen and chemokine receptors in T cells.

L6 ANSWER 7 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004438925 EMBASE
TITLE: The chemokine network in cancer - Much more than directing cell movement.
AUTHOR: Kulbe H.; Levinson N.R.; Balkwill F.; Wilson J.L.
CORPORATE SOURCE: Dr. J.L. Wilson, Cancer Research UK, Translational Oncology Laboratory, Qu. Mary's Sch. of Med. and Dent., Charterhouse Square, London, EC1M 6BQ, United Kingdom. julia.wilson@cancer.org.uk
SOURCE: International Journal of Developmental Biology, (2004) 48/5-6 (489-496).
Refs: 83
ISSN: 0214-6282 CODEN: IJDBE5
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cytokine and chemokine gradients are central to the directed movement of cells in both homeostatic and pathological processes. Most cancers have a complex chemokine network which can influence immune responses to the tumor, direct the extent and cellular composition of the leukocyte infiltrate and also play a role in angiogenesis. Tumor cells can also hijack the chemokine system and gain expression of certain chemokine receptors and respond to specific chemokine gradients. Chemokine receptor expression and activation on malignant cells may be central to the growth, survival and migration of cancer cells from the primary tumor. Chemokine receptors, both CC and CXC have been detected on malignant cells and the relevant ligands are sometimes expressed at the tumor site and at sites of tumor spread, suggesting a role for the chemokine family in malignant growth and metastasis.

L6 ANSWER 8 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004390846 EMBASE
TITLE: CXCR4-mediated adhesion and MMP-9 secretion in head and

neck squamous cell carcinoma.
AUTHOR: Samara G.J.; Lawrence D.M.; Chiarelli C.J.; Valentino M.D.; Lyubsky S.; Zucker S.; Vaday G.G.
CORPORATE SOURCE: . gayle.vaday@med.va.gov
SOURCE: Cancer Letters, (28 Oct 2004) 214/2 (231-241).
Refs: 33
ISSN: 0304-3835 CODEN: CALEDQ
PUBLISHER IDENT.: S 0304-3835(04)00372-6
COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The chemokine CXCL12 (SDF-1) and its receptor, CXCR4, have been implicated in organ-specific metastases of several malignancies. Head and neck squamous cell carcinoma (HNSCC) predominantly metastasizes to **lymph nodes**, and recent evidence has shown that CXCL12 stimulates HNSCC migration. We explored the potential role of CXCR4 in mediating other metastatic processes in HNSCC cells. CXCR4 mRNA and cell-surface expression was assessed in HNSCC cell lines. CXCR4 mRNA expression was detected in five HNSCC cell lines. Cell-surface CXCR4 was also detected in each of the HNSCC cell lines and in resected HNSCC tissues. CXCL12 induced rapid intracellular calcium mobilization in a metastatic HNSCC cell line (HN), as well as rapid phosphorylation of ERK-1/2. HNSCC cell adhesion to fibronectin and collagen was increased by CXCL12 treatment, while the addition of an inhibitor of ERK-1/2 signaling, PD98059, reduced the effects of CXCL12. CXCL12 also increased the active matrix metalloproteinase (MMP)-9 secreted. Thus, HNSCC cells express functional CXCR4 receptors that induce rapid intracellular signaling upon binding to CXCL12. Such binding leads to increased HNSCC cell adhesion and MMP secretion, suggesting that CXCR4 may be a novel regulator of HNSCC metastatic processes. .COPYRGT. 2004 Elsevier Ireland Ltd. All rights reserved.

L6 ANSWER 9 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:288935 BIOSIS
DOCUMENT NUMBER: PREV200400287692
TITLE: Differential TNFR and LT beta R regulation of High Endothelial Venule (HEV) Specific Genes.
AUTHOR(S): Liao, Shan [Reprint Author]; Lesslauer, Werner; Ruddle, Nancy H
CORPORATE SOURCE: Epidemiology and Public Health, Yale University School of Medicine, 60 College Street, New Haven, CT, 06520-8034, USA shan.liao@yale.edu
SOURCE: FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 332.1. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004
AB HEVs are specialized **lymph node** blood vessels where lymphocyte trafficking occurs. Optimal HEV function may be regulated at the level of gene expression of glycoproteins (GlyCAM-1, MAdCAM-1), chemokines (SLC) and posttranslational modifying enzymes (FucTIV, FucTVII, and an HEV specific GlcNAc-6-sulfotransferase (HEC-6ST)). We have previously determined that LTbR signaling contributes to HEV and HEC6ST in LTb-/- and in RIPLTab transgenic mice. Both the classical and alternative

NF-kB pathways have been implicated in LTbR signal transduction in fibroblasts and spleen cells. However, it was not clear whether LTab could directly stimulate endothelial cells and/or whether its effect was mediated through **stromal cells**, which in turn activate HEV gene expression. Endothelial cell lines, bEND.3 and SVEC, were adopted as an in vitro system to evaluate and compare LTbR and TNFR mediated signaling for endothelial and HEV specific genes. FACS analysis revealed LTbR surface expression on both cell lines. Several genes were differentially induced by treatment with LTbR agonistic antibody or TNF. The signaling pathways regulating gene expression also differed as revealed by treatment with **kinase** or NF-kB inhibitors. Therefore, LTab has the capacity to directly activate endothelial cells and the pathways and genes differ from those employed by TNF. Supported by NIH CA16885 and the Anna Fuller Fund for Cancer Research.

L6 ANSWER 10 OF 50 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003561148 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14633723
TITLE: Both hepatocyte growth factor (HGF) and stromal-derived factor-1 regulate the metastatic behavior of human rhabdomyosarcoma cells, but only HGF enhances their resistance to radiochemotherapy.
AUTHOR: Jankowski Kacper; Kucia Magda; Wysoczynski Marcin; Reca Ryan; Zhao Dongling; Trzyna Ela; Trent John; Peiper Stephen; Zembala Marek; Ratajczak Janina; Houghton Peter; Janowska-Wieczorek Anna; Ratajczak Mariusz Z
CORPORATE SOURCE: Stem Cell Biology Program, James Graham Brown Cancer Center, University of Louisville, 529 South Jackson Street, Louisville, KY 40202, USA.
CONTRACT NUMBER: 3P0 SE 10122 (NHLBI)
R01 HL 61796-01
SOURCE: Cancer research, (2003 Nov 15) 63 (22) 7926-35.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040210
Entered Medline: 20040209

AB Rhabdomyosarcomas (RMSs) are frequently characterized by bone marrow involvement. Recently, we reported that human RMS cells express the CXC chemokine receptor-4 (CXCR4) and postulated a role for the CXCR4 stromal-derived factor (SDF)-1 axis in the metastasis of RMS cells to bone marrow. Because RMS cells also express the tyrosine **kinase** receptor c-MET, the specific ligand hepatocyte growth factor (HGF) that is secreted in bone marrow and **lymph node** stroma, we hypothesized that the c-MET-HGF axis modulates the metastatic behavior of RMS cells as well. Supporting this concept is our observation that conditioned media harvested from expanded ex vivo human bone marrow fibroblasts chemoattracted RMS cells in an HGF- and SDF-1-dependent manner. Six human alveolar and three embryonal RMS cell lines were examined. We found that although HGF, similar to SDF-1, did not affect the proliferation of RMS cells, it induced in several of them: (a) locomotion; (b) stress fiber formation; (c) chemotaxis; (d) adhesion to human umbilical vein endothelial cells; (e) trans-Matrigel invasion and matrix metalloproteinase secretion; and (f) phosphorylation of mitogen-activated protein **kinase** p42/44 and AKT. Moreover HGF, but not SDF-1, increased the survival of RMS cells exposed to radio- and chemotherapy. We also found that the more aggressive alveolar RMS cells express higher levels of c-MET than embryonal RMS cell lines and "home/seed" better into bone marrow after i.v. injection into immunocompromised mice. Because we could not find any activating

mutations in the **kinase** region of c-MET or any evidence for HGF autocrine stimulation, we suggest that the increased response of RMS cell lines depends on overexpression of functional c-MET. We conclude that HGF regulates the metastatic behavior of c-MET-positive RMS cells, directing them to the bone marrow and **lymph nodes**. Signaling from the c-MET receptor may also contribute to the resistance of RMS cells to conventional treatment modalities.

L6 ANSWER 11 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003453008 EMBASE
TITLE: Axis of evil: Molecular mechanisms of cancer metastasis.
AUTHOR: Bogenrieder T.; Herlyn M.
CORPORATE SOURCE: M. Herlyn, Wistar Institute, 3601 Spruce Street, Philadelphia, PA 19104, United States. herlynm@wistar.upenn.edu
SOURCE: Oncogene, (2 Oct 2003) 22/43 (6524-6536).
Refs: 142
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Although the genetic basis of tumorigenesis may vary greatly between different cancer types, the cellular and molecular steps required for metastasis are similar for all cancer cells. Not surprisingly, the molecular mechanisms that propel invasive growth and metastasis are also found in embryonic development, and to a less perpetual extent, in adult tissue repair processes. It is increasingly apparent that the stromal microenvironment, in which neoplastic cells develop, profoundly influences many steps of cancer progression, including the ability of tumor cells to metastasize. In carcinomas, the influences of the microenvironment are mediated, in large part, by bidirectional interactions (adhesion, survival, proteolysis, migration, immune escape mechanisms lymph-/angiogenesis, and homing on target organs) between epithelial tumor cells and neighboring **stromal cells**, such as fibroblasts as well as endothelial and immune cells. In this review, we summarize recent advances in understanding the molecular mechanisms that govern this frequently lethal metastatic progression along an axis from primary tumor to regional **lymph nodes** to distant organ sites. Affected proteins include growth factor signaling molecules, chemokines, cell-cell adhesion molecules (cadherins, integrins) as well as extracellular proteases (matrix metalloproteinases). We then discuss promising new therapeutic approaches targeting the microenvironment. We note, however, that there is still too little knowledge of how the many events are coordinated and integrated by the cancer cell, with conspiratorial help by the stromal component of the host. Before drug development can proceed with a legitimate chance of success, significant gaps in basic knowledge need to be filled.

L6 ANSWER 12 OF 50 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2004-00219 BIOTECHDS
TITLE: Suppression of met expression: A possible cancer treatment; potential prostate cancer gene therapy involving use of ribozyme against receptor protein-tyrosine-**kinase**
AUTHOR: SHINOMIYA N; WOUDE GFV
CORPORATE SOURCE: Van Andel Res Inst
LOCATION: Shinomiya N, Van Andel Res Inst, Oncol Mol Lab, 333 Bostwick NE, Grand Rapids, MI 49503 USA
SOURCE: CLINICAL CANCER RESEARCH; (2003) 9, 14, 5085-5090
ISSN: 1078-0432

DOCUMENT TYPE: Journal
LANGUAGE: English
AB DERWENT ABSTRACT: Met is a receptor protein-tyrosine-**kinase** (EC-2.7.1.112) and the only known receptor for HGF/SF. This ligand/receptor signaling pair mediates a vast range of biological activities not only in normal organ development and physiological functions but also in tumor proliferation, progression, invasion, and metastasis. Tumor cells that express high levels of Met molecules on their surface are more malignant and metastatic. In many carcinomas, HGF/SF acting in a paracrine manner is produced by **stromal cells** adjacent to the tumor. Inhibition of Met expression suppresses the malignant progression of tumor cells. A ribozyme strategy has been used to suppress the growth of human glioblastorna tumors. Because overexpression of Met receptors is observed in a wide spectrum of carcinomas and considered to play a key role in the progression of cancer cells, targeting of this molecule could become one of the most useful treatment modalities for refractory cancers. Molecular targeting of the Met signaling pathways by using specifically designed genes. which target c-met, can be used as a treatment modality for controlling tumor growth and metastasis. An adeno virus vector expressing c-Met ribozyme inhibits tumorigenicity and **lymph node** metastasis of human prostate cancer cells by using an orthotopically implanted in vivo mouse model. In prostate cancer cells especially, high expression of Met is associated with resistance against chemotherapy including hormonal therapy and is often observed in the advanced stages of clinical cases. By reducing Met expression using a ribozyme that targets Met mRNA, tumor growth and **lymph node** metastasis were dramatically inhibited(6 pages)

L6 ANSWER 13 OF 50 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003543598 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12881311
TITLE: Complexity within the plasma cell compartment of mice deficient in both E- and P-selectin: implications for plasma cell differentiation.
AUTHOR: Underhill Gregory H; Kolli K Pallav; Kansas Geoffrey S
CORPORATE SOURCE: Department of Microbiology-Immunology, Northwestern Medical School, 303 E Chicago Ave, Chicago, IL 60611, USA.
CONTRACT NUMBER: HL58710 (NHLBI)
SOURCE: Blood, (2003 Dec 1) 102 (12) 4076-83.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031119
Last Updated on STN: 20040115
Entered Medline: 20040114
AB Antibody-secreting plasma cells represent the critical end-stage effector cells of the humoral immune response. Here, we show that several distinct plasma cell subsets are concurrently present in the **lymph nodes**, spleen, and bone marrow of mice deficient in both E- and P-selectin. One of these subsets was a B220-negative immunoglobulin g (IgG) plasma cell population expressing low to negative surface levels of syndecan-1. Examination of the chemotactic responsiveness of IgG plasma cell subsets revealed that migration toward **stromal cell** -derived factor 1/CXC ligand 12 (SDF-1/CXCL12) was primarily limited to the B220-lo subset regardless of tissue source. Although B220-negative plasma cells did not migrate efficiently in response to CXCL12 or to other chemokines for which receptor mRNA was expressed, these cells expressed substantial surface CXC chemokine receptor-4 (CXCR4), and CXCL12 stimulation rapidly induced extracellular signal regulated **kinase** 1 (ERK1)/ERK2 phosphorylation, demonstrating that CXCR4 retained signaling

capacity. Therefore, B220-negative plasma cells exhibit a selective uncoupling of chemokine receptor expression and signaling from migration. Taken together, our findings document the presence of significant heterogeneity within the plasma cell compartment, which suggests a complex step-wise scheme of plasma cell differentiation in which the degree of differentiation and tissue location can influence the chemotactic responsiveness of IgG plasma cells.

L6 ANSWER 14 OF 50 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:330364 SCISEARCH
THE GENUINE ARTICLE: 664NP
TITLE: Expression of vascular endothelial growth factor (VEGF)-D and its receptor, VEGF receptor 3, as a prognostic factor in endometrial carcinoma
AUTHOR: Yokoyama Y (Reprint); Charnock-Jones D S; Licence D; Yanaihara A; Hastings J M; Holland C M; Emoto M; Sakamoto A; Sakamoto T; Maruyama H; Sato S; Mizunuma H; Smith S K
CORPORATE SOURCE: Hirosaki Univ, Sch Med, Dept Obstet & Gynecol, 5 Zaifu Cho, Hirosaki, Aomori 0368562, Japan (Reprint); Hirosaki Univ, Sch Med, Dept Obstet & Gynecol, Hirosaki, Aomori 0368562, Japan; Univ Cambridge, Dept Pathol, Reprod Mol Res Grp, Cambridge CB2 1QP, England
COUNTRY OF AUTHOR: Japan; England
SOURCE: CLINICAL CANCER RESEARCH, (APR 2003) Vol. 9, No. 4, pp. 1361-1369.
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA.
ISSN: 1078-0432.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: To evaluate the prognostic value of vascular endothelial growth factor (VEGF)-D and VEGF receptor (VEGFR)-3 in endometrial carcinoma.

Experimental Design: We assessed the levels of immunoreactivity for VEGF-D and VEGFR-3 in 71 endometrial carcinomas, 14 complex atypical endometrial hyperplasias, and 16 normal endometria by immunohistochemistry.

Results: VEGF-D was stained in both tumor cells and adjacent **stromal cells**. VEGFR-3 was stained in both tumor cells and adjacent endothelial cells. Immunoreactivity for VEGF-D in tumor cells and adjacent **stromal cells** became significantly stronger as lesions progressed from normal endometrium to advanced carcinoma. Similarly, immunoreactivity for VEGFR-3 in tumor cells and adjacent endothelial cells was significantly greater as lesions progressed from normal endometrium to advanced carcinoma. A strong correlation was found between high levels of VEGF-D immunoreactivity in carcinoma cells and VEGFR-3 in both carcinoma cells and adjacent endothelial cells. Similarly, high levels of VEGF-D immunoreactivity in **stromal cells** were significantly correlated with those of VEGFR-3 in both carcinoma cells and endothelial cells. High levels of VEGF-D in carcinoma cells and **stromal cells**, as well as those of VEGFR-3 in carcinoma cells and endothelial cells, were significantly related to myometrial invasion and **lymph node** metastasis. A strong correlation was found between poor survival and high levels of VEGF-D in both carcinoma cells and **stromal cells** and between poor survival and high levels of VEGFR-3 in carcinoma cells. Moreover, the high levels of VEGF-D in **stromal cells** and VEGFR-3 in carcinoma cells were independent prognostic factors in endometrial carcinoma.

Conclusions: The presence of VEGF-D and VEGFR-3 in endometrial carcinoma may predict myometrial invasion and **lymph node**

metastasis and may prospectively identify patients who are at increased risk for poor outcome. In addition, VEGF-D and VEGFR-3 may be promising targets for new therapeutic strategies in endometrial carcinoma.

L6 ANSWER 15 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:153519 BIOSIS
DOCUMENT NUMBER: PREV200400148159
TITLE: Roles of PLC-beta2, -beta3, and PI3K in T-cell migration to SDF 1-alpha.
AUTHOR(S): Bach, Tami L. [Reprint Author]; Chen, Qing-Min [Reprint Author]; Jordan, Martha S.; Wu, Dianqing; Zigmond, Sally H.; Abrams, Charles S. [Reprint Author]
CORPORATE SOURCE: Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 768a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Chemokines bind G-protein coupled receptors and play an essential role in both the immune and inflammatory responses. In T lymphocytes, little is known about the signaling pathways required for chemokine-mediated cell migration. Phospholipase C (PLC) and phosphatidylinositol 3-**kinase** (PI3K) are two distinct signaling molecules that have been proposed as potential candidates in the regulation of this process. Studies with knockout mice have demonstrated a critical role for D3-phosphoinositide production by PI3Kgamma in Galphai-coupled receptor-mediated neutrophil chemotaxis. Similar studies have failed to demonstrate a role for IP3 or DAG production by PLCbeta in this neutrophil response. In the current investigation, peripheral T-cells were isolated from the **lymph nodes** of wild type mice and mice with loss-of-function mutations of either PI3Kgamma, or both of the two dominant lymphocyte PLCbeta isoforms (PLCbeta2 and PLCbeta3). Using a transwell assay, migration of lymphocytes toward SDF-1alpha (37.5 nM) was quantitated after 3 hours, the time point at which migration was maximal for both wild type and knockout T-cells. We found that lymphocytes isolated from wild type mice exhibited an eighteen-fold increase in migration with SDF-1alpha stimulation compared to baseline. In contrast, loss of either PLCbeta2beta3 or PI3Kgamma decreased chemokine-stimulated T-cell migration by 68%+-14% ($p<0.005$) and 12+-4% ($p<0.5$), respectively. The impaired sensitivity of the PLCbeta2/beta3-null T-cells occurred over a wide range of agonist, and in contrast to wild type lymphocytes, a large percentage of migration in the PLCbeta2/beta3-null T-cells was due to SDF-induced chemokinesis and not chemotaxis. Chelation of intracellular calcium by BAPTA (30 nM) decreased the chemotactic response of wild type lymphocytes, but pharmacologic inhibition of PKC isoforms by GF109203x (5 muM) or Go 6976 (5 muM) did not impair T-cell migration. Furthermore, SDF-1alpha-induced calcium efflux was not detected in the PLCbeta2beta3-null lymphocytes. This suggests that the T-cell migration defect seen in the PLCbeta2/beta3-null T-cells may be due to an impaired ability to increase intracellular calcium, while there appears to be little requirement for the stimulation of PKC. We have also found that inhibition of PI3K by either wortmannin (100 nM) or LY294002 (50 muM), decreased SDF-1alpha-induced migration of wild type cells to near baseline, suggesting that PI3K does contribute to T-cell migration, but the PI3Kgamma isoform contributes relatively little to this process.

These results show that in vivo phospholipid second messengers generated by PLCbeta and isoforms of PI3K, other than PI3Kgamma, play a critical role in lymphocyte chemotaxis. Our data demonstrate that although PLCbeta-mediated signaling plays no role in neutrophil chemotaxis, it makes a substantial contribution to this process within T lymphocytes.

L6 ANSWER 16 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:451651 BIOSIS
DOCUMENT NUMBER: PREV200300451651
TITLE: Involvement of **stromal cell**-derived factor-1/CXCR4 signaling in **lymph node** metastasis of oral squamous cell carcinoma.
AUTHOR(S): Uchida, Daisuke [Reprint Author]; Begum, Nasima-Mila; Almofti, Ammar; Kawamata, Hitoshi; Nakashiro, Koh-Ichi; Tateishi, Yoshihisa; Hamakawa, Hiroyuki; Yoshida, Hideo; Sato, Mitsunobu
CORPORATE SOURCE: 2nd Dept. Oral and Maxillofacial Surgery, School of Dentistry, Tokushima University, Tokushima, Japan
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 452. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

L6 ANSWER 17 OF 50 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:930083 SCISEARCH
THE GENUINE ARTICLE: 736BT
TITLE: Differential gene expression in pristane-induced arthritis susceptible DA versus resistant E3 rats
AUTHOR: Wester L (Reprint); Koczan D; Holmberg J; Olofsson P; Thiesen H J; Holmdahl R; Ibrahim S
CORPORATE SOURCE: Lund Univ, BMC, Biomed Ctr, Lund, Sweden (Reprint); Univ Rostock, Inst Immunol, Rostock, Germany
COUNTRY OF AUTHOR: Sweden; Germany
SOURCE: ARTHRITIS RESEARCH & THERAPY, (OCT 2003) Vol. 5, No. 6, pp. R361-R372.
Publisher: BIOMED CENTRAL LTD, MIDDLESEX HOUSE, 34-42 CLEVELAND ST, LONDON W1T 4LB, ENGLAND.
ISSN: 1478-6362.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 45
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Arthritis susceptibility genes were sought by analysis of differential gene expression between pristane-induced arthritis (PIA)-susceptible DA rats and PIA-resistant E3 rats. Inguinal **lymph nodes** of naive animals and animals 8 days after pristane injection were analyzed for differential gene expression. mRNA expression was investigated by microarray and real-time PCR, and protein expression was analyzed by flow cytometry or ELISA. Twelve genes were significantly differentially expressed when analyzed by at least two independent methods, and an additional five genes showed a strong a tendency toward differential expression. In naive DA rats IgE, the bone marrow **stromal cell** antigen 1 (Bst1) and the MHC class II beta-chain (MhcII) were expressed at a higher level, and the immunoglobulin kappa chain (Igkappa) was expressed at a lower level. In pristane-treated DA rats the MHC class

II beta-chain, gelatinase B (Mmp9) and the protein tyrosine phosphatase CL100 (Ptpn16) were expressed at a higher level, whereas immunoglobulins, the CD28 molecule (Cd28), the mast cell specific protease 1 (Mcpt1), the carboxylesterase precursor (Ces2), K-cadherin (Cdh6), cyclin G1 (Ccng1), DNA polymerase IV (Primase) and the tumour associated glycoprotein E4 (Tage) were expressed at a lower level. Finally, the differentially expressed mRNA was confirmed with protein expression for some of the genes. In conclusion, the results show that animal models are well suited for reproducible microarray analysis of candidate genes for arthritis. All genes have functions that are potentially important for arthritis, and nine of the genes are located within genomic regions previously associated with autoimmune disease.

L6 ANSWER 18 OF 50 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003491192 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14567988
TITLE: Possible role of **stromal-cell**-derived factor-1/CXCR4 signaling on **lymph node** metastasis of oral squamous cell carcinoma.
AUTHOR: Uchida Daisuke; Begum Nasima Mila; Almofti Ammar; Nakashiro Koh-ichi; Kawamata Hitoshi; Tateishi Yoshihisa; Hamakawa Hiroyuki; Yoshida Hideo; Sato Mitsunobu
CORPORATE SOURCE: Second Department of Oral and Maxillofacial Surgery, Tokushima University School of Dentistry, 3-18-15 Kuramoto, Tokushima 770-8504, Japan.. daisuke@dent.tokushima-u.ac.jp
SOURCE: Experimental cell research, (2003 Nov 1) 290 (2) 289-302. Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031022
Last Updated on STN: 20031219
Entered Medline: 20031202
AB We examined the role of chemokine signaling on the **lymph node** metastasis of oral squamous cell carcinoma (SCC) using **lymph node** metastatic (HNt and B88) and nonmetastatic oral SCC cells. Of 13 kinds of chemokine receptors examined, only CXCR4 expression was up-regulated in HNt and B88 cells. CXCR4 ligand, **stromal-cell**-derived factor-1alpha (SDF-1alpha; CXCL12), induced characteristic calcium fluxes and chemotaxis only in CXCR4-expressing cells. CXCR4 expression in metastatic cancer tissue was significantly higher than that in nonmetastatic cancer tissue or normal gingiva. Although SDF-1alpha was undetectable in either oral SCC or normal epithelial cells, submandibular **lymph nodes** expressed the SDF-1alpha protein, mainly in the **stromal cells**, but occasionally in metastatic cancer cells. The conditioned medium from lymphatic **stromal cells** promoted the chemotaxis of B88 cells, which was blocked by the CXCR4 neutralization. SDF-1alpha rapidly activated extracellular signal-regulated **kinase** (ERK)1/2 and Akt/protein **kinase** B (PKB), and their synthetic inhibitors attenuated the chemotaxis by SDF-1alpha. SDF-1alpha also activated Src family **kinases** (SFKs), and its inhibitor PP1 diminished the SDF-1alpha-induced chemotaxis and activation of both ERK1/2 and Akt/PKB. These results indicate that SDF-1/CXCR4 signaling may be involved in the establishment of **lymph node** metastasis in oral SCC via activation of both ERK1/2 and Akt/PKB induced by SFKs.

L6 ANSWER 19 OF 50 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2003125665 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12639303
TITLE: Phase I dose escalation clinical trial of adenovirus vector

carrying osteocalcin promoter-driven herpes simplex virus thymidine **kinase** in localized and metastatic hormone-refractory prostate cancer.

AUTHOR: Kubo Hiroyuki; Gardner Thomas A; Wada Yoshitaka; Koeneman Kenneth S; Gotoh Akinobu; Yang Ling; Kao Chinghai; Lim So Dug; Amin Mahul B; Yang Hua; Black Margaret E; Matsubara Shigeji; Nakagawa Masayuki; Gillenwater Jay Y; Zhau Haiyen E; Chung Leland W K

CORPORATE SOURCE: Department of Urology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, USA.

CONTRACT NUMBER: CA-79544-01A2 (NCI)
CA-85555 (NCI)

SOURCE: Human gene therapy, (2003 Feb 10) 14 (3) 227-41.
Journal code: 9008950. ISSN: 1043-0342.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310

ENTRY DATE: Entered STN: 20030318
Last Updated on STN: 20031008
Entered Medline: 20031006

AB Osteocalcin (OC), a major noncollagenous bone matrix protein, is expressed prevalently in prostate cancer epithelial cells, adjacent fibromuscular **stromal cells**, and osteoblasts in locally recurrent prostate cancer and prostate cancer bone metastasis [Matsubara, S., Wada, Y., Gardner, T.A., Egawa, M., Park, M.S., Hsieh, C.L., Zhau, H.E., Kao, C., Kamidono, S., Gillenwater, J.Y., and Chung, L.W. (2001). Cancer Res. 61, 6012-6019]. We constructed an adenovirus vector carrying osteocalcin promoter-driven herpes simplex virus thymidine **kinase** (Ad-OC-hsv-TK) to cotarget prostate cancer cells and their surrounding **stromal cells**. A phase I dose escalation clinical trial of the intralesional administration of Ad-OC-hsv-TK followed by oral valacyclovir was conducted at the University of Virginia (Charlottesville, VA) in 11 men with localized recurrent and metastatic hormone-refractory prostate cancer (2 local recurrent, 5 osseous metastasis, and 4 **lymph node** metastasis) in order to determine the usefulness of this vector for the palliation of androgen-independent prostate cancer metastasis. This is the first clinical trial in which therapeutic adenoviruses are injected directly into prostate cancer **lymph node** and bone metastasis. Results show that (1). all patients tolerated this therapy with no serious adverse events; (2). local cell death was observed in treated lesions in seven patients (63.6%) as assessed by TUNEL assay, and histomorphological change (mediation of fibrosis) was detected in all posttreated specimens; (3). one patient showed stabilization of the treated lesion for 317 days with no alternative therapy. Of the two patients who complained of tumor-associated symptoms before the treatment, one patient with bone pain had resolution of pain, although significant remission of treated lesions was not observed by image examination; (4). CD8-positive T cells were predominant compared with CD4-positive T cells, B cells (L26 positive), and natural killer cells (CD56 positive) in posttreated tissue specimens; (5). levels of HSV TK gene transduction correlated well with coxsackie-adenovirus receptor expression but less well with the titers of adenovirus injected; and (6). intrinsic OC expression and the efficiency of HSV TK gene transduction affected the levels of HSV TK protein expression in clinical specimens. Our data suggest that this form of gene therapy requires further development for the treatment of androgen-independent prostate cancer metastasis although histopathological and immunohistochemical evidence of apoptosis was observed in the specimens treated. Further studies including the development of viral delivery will enhance the efficacy of Ad-OC-hsv-TK.

L6 ANSWER 20 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:168136 BIOSIS
DOCUMENT NUMBER: PREV200400162042
TITLE: Synergistic effect of epidermal growth factor receptor and chemokine receptor CXCR4 in tumor metastasis.
AUTHOR(S): Wang, Zixuan [Reprint Author]; Dziedziejko, Violetta [Reprint Author]; Navenot, Jean-Marc D. [Reprint Author]; Peiper, Stephen C. [Reprint Author]
CORPORATE SOURCE: Department of Pathology, Medical College of Georgia, Augusta, GA, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 171b. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004

AB Elucidation of the fundamental mechanisms involved in tumor metastasis remains an important research priority and will lead to the development of novel treatment strategies. The major sites of breast cancer metastasis are regional **lymph nodes**, lung, liver, and bone marrow, and each has been shown to secrete **stromal cell** derived factor 1 (SDF-1), a member of the chemokine superfamily. The expression of CXCR4, the specific receptor for SDF-1 by breast cancer cell lines, and the finding that blockade of CXCR4 by its specific antibody inhibited metastatic spread in a xenograft model led to the recognition that a chemoattactant mechanism is involved in determining the organ-selective pattern of breast cancer metastases. Clinical data, on the other hand, indicate a strong association between activation of receptor tyrosine **kinases**, such as the epidermal growth factor (EGF) receptor (EGFR) and HER-2/neu, and the metastatic spread of tumor malignancy. To gain insight into the role of EGFR and CXCR4 in metastatic spread, HeLa cells that express functional CXCR4 and high levels of EGFR were used as a model of tumor cells in chemotaxis experiments. The chemotaxis of HeLa cells induced by SDF-1 was significantly increased when they were co-exposed to EGF, either in the top or bottom of standard transwell chambers. This synergism was completely inhibited by T140, a specific CXCR4 antagonist, or pertussis toxin. EGF alone induced chemokinesis, but not chemotaxis. Exposure of HeLa cells to EGF did not alter levels of CXCR4 on the cell surface. Since EGFR and CXCR4 signaling pathways both activate phosphatidylinositol 3-**kinase** (PI3-K), the induction of phosphorylation of Akt, a downstream target of this **kinase**, by SDF-1 in the presence and absence of EGF was determined by Western blotting. Cells incubated with both SDF-1 and EGF had a synergistic increase in Akt phosphorylation in comparison to those treated only with the chemokine or the growth factor. PI3-K antagonists blocked this effect and also inhibited directional migration of HeLa cells. These findings provide direct evidence for cross talk between RTK and GPCR pathways. They suggest that the role of CXCR4 in programming the metastatic spread of malignant cells may be regulated by RTKs. Thus, CXCR4 may be a suitable target for the blockade of metastatic spread in malignancies, particularly in those that overexpress RTKs.

L6 ANSWER 21 OF 50 MEDLINE on STN

ACCESSION NUMBER: 2003003088 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12393730
TITLE: CCR7-mediated physiological lymphocyte homing involves activation of a tyrosine **kinase** pathway.

AUTHOR: Stein Jens V; Soriano Silvia F; M'rini Christine; Nombela-Arrieta Cesar; de Buitrago Gonzalo Gonzalez; Rodriguez-Frade Jose Miguel; Mellado Mario; Girard Jean-Philippe; Martinez-A Carlos
CORPORATE SOURCE: Department of Immunology and Oncology, Centro Nacional de Biotecnologia/Consejo Superior de Investigaciones Cientificas (CSIC), Madrid, Spain.. jstein@cnb.uam.es
SOURCE: Blood, (2003 Jan 1) 101 (1) 38-44.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030103
Last Updated on STN: 20030331
Entered Medline: 20030318

AB Homing of blood-borne lymphocytes to peripheral **lymph nodes** (PLNs) is a multistep process dependent on the sequential engagement of L-selectin, which mediates lymphocyte rolling along the luminal surface of high endothelial venules (HEVs), followed by activation of lymphocyte integrins and transmigration through HEVs. Within lymphoid tissue, B and T lymphocytes then migrate toward specific microenvironments such as B-cell follicles and the paracortex, respectively. The lymphocyte-expressed chemokine receptor CCR7 is playing an important role during this process, as its HEV-presented ligands CCL19 and CCL21 can trigger rapid integrin activation under flow in addition to inducing a chemotactic response, which may participate in transmigration and/or interstitial migration. Here, we report that Tyrphostin (Tyr) AG490, a pharmacological inhibitor of Janus family tyrosine **kinases** (Jaks), blocked the chemotactic response of primary mouse lymphocytes to CCL19 and CCL21 in a dose-dependent manner. Furthermore, Tyr AG490 inhibited rapid CCL21-mediated up-regulation of alpha4 and beta2 integrin adhesiveness in static adhesion assays and under physiological flow, whereas adhesion induced by phorbol myristate acetate remained unaltered. Using intravital microscopy of subiliac PLNs in mice, we found that adoptively transferred Tyr AG490-treated lymphocytes adhered significantly less in HEVs compared with control cells, although L-selectin-mediated rolling was similar in both samples. Finally, we observed rapid Jak2 phosphorylation in CCL21-stimulated primary mouse lymphocytes. Thus, our study suggests a role for Jak tyrosine **kinases** during CCR7-mediated lymphocyte recirculation.

L6 ANSWER 22 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:120036 HCAPLUS
DOCUMENT NUMBER: 138:236622
TITLE: RelB in secondary lymphoid organ development: differential regulation by lymphotoxin and tumor necrosis factor signaling pathways
AUTHOR(S): Yilmaz, Z. Buket
CORPORATE SOURCE: Institut fuer Toxikologie und Genetik, Germany
SOURCE: Wissenschaftliche Berichte - Forschungszentrum Karlsruhe (2002), FZKA 6793, i-xv, 1-117
CODEN: WBFKF5; ISSN: 0947-8620
DOCUMENT TYPE: Report
LANGUAGE: English

AB Primary lymphoid organs are the major sites of lymphopoiesis where lymphocytes proliferate and mature into functional but naive cells. Secondary lymphoid organs are sites where these lymphocytes encounter antigens and elicit immune responses. RelB is a member of the Rel/NF-κB family of inducible dimeric transcription factors. RelB is abundantly expressed in secondary lymphoid organs, such as spleen, **lymph nodes**, and Peyer's patches (PP). RelB-deficient mice have improper spleen structure and lack organizing centers for PPs,

defects that can not be restored by the adoptive transfer of wild-type bone marrow cells. The work presented here revealed a reduction in expression of the homing chemokines B lymphocyte chemoattractant (BLC) and secondary lymphoid organ chemokine (SLC) in RelB-deficient spleen, suggesting a role for RelB in proper expression of chemokines by splenic **stromal cells**. Moreover, interleukin-7 (IL-7)-induced expression of lymphotoxin (LT) in intestinal cells, a crucial step in early PP development, was not impaired in RelB-deficient embryos, suggesting functional hematopoietic inducers and a defect in LTβ receptor (LTβR) expressing stromal responders. Activation of LTβR signaling in fibroblasts resulted in the specific induction of p52-RelB heterodimers, while tumor necrosis factor (TNF) induced classical p50-RelA NF-κB complexes. LTβR-induced RelB nuclear translocation and DNA binding of p52-RelB heterodimers required the degradation of the inhibitory p52 precursor, p100, which was dependent on the IκB **kinase** (IKK) complex subunit IKKα, but not on IKKβ or IKKγ. In contrast to LTβR signaling, TNFR signaling increased p100 and RelB levels both in cytoplasm and nucleus and RelB was bound to p100 in both compartments. Despite the abundant presence of RelB in the nucleus, RelB DNA binding was almost undetectable in TNF treated fibroblasts. Forced expression of p50 and p52 could not rescue the lack of DNA binding. In contrast, RelB DNA binding increased in cells lacking the C-terminus of p100, but not of p105, strongly suggesting that it is the specific inhibitory function of the C-terminal domain of p100, rather than the lack of the heterodimerization partner, which prevents RelB DNA binding in TNF-stimulated fibroblasts. Thus, RelB and p52 in **stromal cells** could function in the proper development of the spleen by regulating the expression of chemokines such as BLC. Furthermore, generation of p52-RelB heterodimers by the LTβR pathway involving p100 degradation, appears to be a critical step in the formation of PP anlage.

REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 23 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:602742 BIOSIS
DOCUMENT NUMBER: PREV200200602742
TITLE: Regulation of cellular proliferation, cytoskeletal function, and signal transduction through CXCR4 and c-Kit in small cell lung cancer cells.
AUTHOR(S): Kijima, Takashi; Maulik, Gautam; Ma, Patrick C.; Tibaldi, Elena V.; Turner, Ross E.; Rollins, Barrett; Sattler, Martin; Johnson, Bruce E.; Salgia, Ravi [Reprint author]
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Dana 1234B, Boston, MA, 02115, USA ravi_salgia@dfci.harvard.edu
SOURCE: Cancer Research, (November 1, 2002) Vol. 62, No. 21, pp. 6304-6311. print.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Nov 2002
Last Updated on STN: 27 Nov 2002

AB The regulation of biological functions including cell growth, viability, migration, and adhesion of small cell lung cancer (SCLC) cells depends largely on the autocrine or paracrine stimulation of growth factor receptors and chemokine receptors. Stem cell factor (SCF) and its receptor c-Kit have been identified as important regulators of SCLC viability and are coexpressed in approximately 40-70% of SCLC specimens. In vitro, the inhibition of c-Kit tyrosine **kinase** activity by the small molecule tyrosine **kinase** inhibitor STI571 (Gleevec)

abrogates cell growth. We have investigated the role of c-Kit and chemokine receptors in the regulation of cell migration and adhesion of SCLC cells. CXCR4, the chemokine receptor for **stromal cell**-derived factor-1alpha (SDF-1alpha), was found to be the major chemokine receptor commonly expressed in all of the 10 SCLC cell lines tested. SCF and SDF-1alpha increased cellular proliferation over a course of 72 h in both the c-Kit- and the CXCR4-positive NCI-H69 SCLC cell line. Recently, SDF-1alpha and CXCR4 have been shown to be important regulators of migration and metastasis in breast and ovarian cancer. We found that SDF-1alpha dramatically increased cell motility and adhesion in CXCR4-expressing NCI-H446 SCLC cells. In addition, SDF-1alpha altered cell morphology with increased formation of filopodia and neurite-like projections. In NCI-H69 SCLC cells, SCF and SDF-1alpha cooperatively induced morphological changes and activated downstream signaling pathways. Treatment of NCI-H69 cells with STI571 specifically inhibited the c-Kit signaling events of Akt and p70 S6 **kinase**, whereas SDF-1alpha-mediated activation of Akt or p70 S6 **kinase** was normal. In contrast, the phosphatidylinositol 3-**kinase** inhibitor, LY294002, prevented these cells from adhering and completely blocked SCF- and/or SDF-1alpha-induced Akt or p70 S6 **kinase** phosphorylation. These results demonstrate that the CXCR4 receptor is functionally expressed in SCLC cells and may, therefore, be involved in the pathogenesis of SCLC in vivo. Inhibition of both the CXCR4 and the c-Kit downstream events could be a promising therapeutic approach in SCLC.

L6 ANSWER 24 OF 50 MEDLINE on STN DUPLICATE 7

ACCESSION NUMBER: 2002496206 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12239174
TITLE: CXCR4-SDF-1 signaling is active in rhabdomyosarcoma cells and regulates locomotion, chemotaxis, and adhesion.
AUTHOR: Libura Jolanta; Drukala Justyna; Majka Marcin; Tomescu Oana; Navenot Jean Marc; Kucia Magda; Marquez Leah; Peiper Stephen C; Barr Frederic G; Janowska-Wieczorek Anna; Ratajczak Mariusz Z
CORPORATE SOURCE: Stem Cell Biology Program at the James Graham Brown Cancer Center, University of Louisville, KY 40202, USA.
CONTRACT NUMBER: 3P05E10122 (NHLBI)
R01 HL61796-01 (NCI)
R01CA64202
SOURCE: Blood, (2002 Oct 1) 100 (7) 2597-606.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021003
Last Updated on STN: 20021217
Entered Medline: 20021205

AB We hypothesized that the CXC chemokine receptor-4 (CXCR4)-stromal-derived factor-1 (SDF-1) axis may be involved in metastasis of CXCR4(+) tumor cells into the bone marrow and **lymph nodes**, which secrete the alpha-chemokine SDF-1. To explore this hypothesis, we phenotyped by fluorescence-activated cell sorter analysis various human tumor cell lines for expression of CXCR4 and found that it was highly expressed on several rhabdomyosarcoma (RMS) cell lines. We also observed that cell lines derived from alveolar RMS, which is characterized by recurrent PAX3- and PAX7-FKHR gene fusions and is associated with a poor prognosis, expressed higher levels of CXCR4 than lines derived from embryonal RMS. Furthermore, transfer of a PAX3-FKHR gene into embryonal RMS cell activates CXCR4 expression. Because alveolar RMS frequently metastasizes to the bone marrow and **lymph nodes**, it seems that the CXCR4-SDF-1 axis could play an important role in this process. These findings prompted us to determine whether SDF-1 regulates

the metastatic behavior of RMS cells. Accordingly, we found that, although SDF-1 did not affect proliferation or survival of these cell lines, it induced in several of them (1) phosphorylation of mitogen-activated protein **kinase** p42/44; (2) locomotion; (3) directional chemotaxis across membranes covered by laminin, fibronectin, or Matrigel; (4) adhesion to laminin, fibronectin, and endothelial cells; and (5) increased MMP-2 and diminished tissue inhibitors of metalloproteinases secretion. The small-molecule CXCR4-specific inhibitor, T140, effectively blocked the in vitro responses of RMS cells to SDF-1. On the basis of these observations we suggest that the CXCR4-SDF-1 axis may play an important role in tumor spread and metastasis of RMS cells to bone marrow and that molecular strategies aimed at inhibiting this axis could thus prove to be useful therapeutic measures.

L6 ANSWER 25 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2002414602 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12168824
TITLE: Expression of the vascular endothelial growth factor receptor-3 (VEGFR-3) and its ligand VEGF-C in human colorectal adenocarcinoma.
AUTHOR: Witte Deborah; Thomas Abraham; Ali Najeeba; Carlson Nicole; Younes Mamoun
CORPORATE SOURCE: Department of Pathology, Baylor College of Medicine and The Methodist Hospital, Houston, TX 77030, USA.
SOURCE: Anticancer research, (2002 May-Jun) 22 (3) 1463-6. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020810
Last Updated on STN: 20020914
Entered Medline: 20020913

AB Vascular endothelial growth factors (VEGF) are secreted by many tumor types, and are believed to affect tumor growth by promoting angiogenesis through binding to their receptors present on vascular endothelium. Recently, mRNA for VEGF-C the ligand for VEGFR-3, was found to be up-regulated in colorectal adenocarcinoma (CRC). The aim of this work was to determine: 1) the distribution of VEGF-C and VEGFR-3 in CRC, and 2) the biological significance of such expression. Sections of formalin-fixed and paraffin-embedded tissues from 56 CRC were immunohistochemically stained for VEGF-C and VEGFR-3. The type and percent of positive cells was recorded. Survival analysis was performed using the Kaplan-Meier method. All CRC were positive for VEGF-C which was present in the cancer cells themselves, as well as in **stromal cells**. Normal colon epithelium was usually negative. Only ten (17%) of the 56 CRC completely lacked VEGFR-3 expression. VEGFR-3 immunoreactivity was detected in <25% of the cancer cells in 22 cases and in >25% of the cells in 34 cases. Expression of VEGFR-3 in >25% of the cancer cells was associated with significantly poorer overall survival ($p<0.05$), but not with **lymph node** metastasis or depth of tumor invasion. Our results suggest that VEGFs promote cancer growth not only by stimulating angiogenesis, but also by acting on receptors present on the cancer cells themselves.

L6 ANSWER 26 OF 50 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2002454843 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12213723
TITLE: Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis.
AUTHOR: Schoppmann Sebastian F; Birner Peter; Stockl Johannes; Kalt Romana; Ullrich Robert; Caucig Carola; Kriehuber Ernst;

Nagy Katalin; Alitalo Kari; Kerjaschki Dontscho
CORPORATE SOURCE: Department of Pathology, University of Vienna-Allgemeines Krankenhaus, Austria.
SOURCE: American journal of pathology, (2002 Sep) 161 (3) 947-56. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020906
Last Updated on STN: 20020928
Entered Medline: 20020927

AB Formation of lymphatic metastasis is the initial step of generalized spreading of tumor cells and predicts poor clinical prognosis. Lymphatic vessels generally arise within the peritumoral stroma, although the lymphangiopoietic vascular endothelial growth factors (VEGF)-C and -D are produced by tumor cells. In a carefully selected collection of human cervical cancers (stage pT1b1) we demonstrate by quantitative immunohistochemistry and in situ hybridization that density of lymphatic microvessels is significantly increased in peritumoral stroma, and that a subset of **stromal cells** express large amounts of VEGF-C and VEGF-D. The density of cells producing these vascular growth factors correlates with peritumoral inflammatory stroma reaction, lymphatic microvessel density, and indirectly with peritumoral carcinomatous lymphangiosis and frequency of **lymph node** metastasis. The VEGF-C- and VEGF-D-producing stroma cells were identified in situ as a subset of activated tumor-associated macrophages (TAMs) by expression of a panel of macrophage-specific markers, including CD68, CD23, and CD14. These TAMs also expressed the VEGF-C- and VEGF-D-specific tyrosine **kinase** receptor VEGFR-3. As TAMs are derived from monocytes in the circulation, a search in peripheral blood for candidate precursors of VEGFR-3-expressing TAMs revealed a subfraction of CD14-positive, VEGFR-3-expressing monocytes, that, however, failed to express VEGF-C and VEGF-D. Only after in vitro incubation with tumor necrosis factor-alpha, lipopolysaccharide, or VEGF-D did these monocytes start to synthesize VEGF-C de novo. In conclusion VEGF-C-expressing TAMs play a novel role in peritumoral lymphangiogenesis and subsequent dissemination in human cancer.

L6 ANSWER 27 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:274544 HCAPLUS
DOCUMENT NUMBER: 137:167190
TITLE: Activation of AKT/PKB in breast cancer predicts a worse outcome among endocrine treated patients
AUTHOR(S): Perez-Tenorio, G.; Stal, O.; Arnesson, L. G.; Malmstrom, A.; Nordenskjold, B.; Nordenskjold, K.; Bang, H.; Kallstrom, A. Ch.; Einarsson, E.; Norberg, B.; Skoog, P.; Henning, A.; Sundquist, M.; Tejler, G.
CORPORATE SOURCE: Southeast Sweden Breast Cancer Group, Department of Biomedicine and Surgery, Division of Oncology, Clinical Research Center, Faculty of Health Sciences, Linkoping University, Linkoping, SE-581 85, Swed.
SOURCE: British Journal of Cancer (2002), 86(4), 540-545 CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Akt/PKB is a serine/threonine protein **kinase** that regulates cell cycle progression, apoptosis and growth factor mediated cell survival in association with tyrosine **kinase** receptors. The protein is a downstream effector of erbB-2 with implications in breast cancer progression and drug resistance in vitro. We aimed to examine the role of Akt-1 in breast cancer patients, by determing whether the expression

(Akt-1) and/or activation (pAkt) were related to prognostic markers and survival. The expression of erbB-2, heregulin β1 and Bcl-2 was also assessed by flow cytometry or immunohistochem. This study comprised 93 patients, aged <50 who were treated with tamoxifen and/or goserelin. We found that pAkt was associated with lower S-phase fraction (P=0.001) and the presence of heregulin β1-expressing **stromal cells** (P=0.017). Neither Akt-1 nor pAkt was related with other factors. Tumor cells-derived heregulin β1 was found mainly in estrogen receptor neg. (P=0.026) and node neg. (P=0.005) cases. Survival anal. revealed that pAkt pos. patients were more prone to relapse with distant metastasis, independently of S-phase fraction and nodal status (multivariate anal.; P=0.004). The results suggest that activation of Akt may have prognostic relevance in breast cancer.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 28 OF 50 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN DUPLICATE 9

ACCESSION NUMBER: 2002:901331 SCISEARCH
THE GENUINE ARTICLE: 609WR
TITLE: Activation of c-Src is inversely correlated with biological aggressiveness of breast carcinoma
AUTHOR: Ito Y; Kawakatsu H; Takeda T; Tani N; Kawaguchi N; Noguchi S; Sakai T; Matsuura N (Reprint)
CORPORATE SOURCE: Osaka Univ, Sch Allied Hlth Sci, Dept Pathol, Fac Med, 1-7 Yamadaoka, Suita, Osaka 5650871, Japan (Reprint); Osaka Univ, Sch Allied Hlth Sci, Dept Pathol, Fac Med, Suita, Osaka 5650871, Japan; Osaka Seamens Insurance Hosp, Dept Surg, Osaka, Japan; Univ Calif San Francisco, Lung Biol Ctr, San Francisco, CA 94143 USA; Osaka Univ, Sch Med, Dept Surg Oncol, Osaka, Japan; Lund Univ, Dept Expt Pathol, Lund, Sweden
COUNTRY OF AUTHOR: Japan; USA; Sweden
SOURCE: BREAST CANCER RESEARCH AND TREATMENT, (DEC 2002) Vol. 76, No. 3, pp. 261-267.
Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS.
ISSN: 0167-6806.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 39

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In order to investigate whether c-Src is involved in carcinogenesis and progression of breast carcinoma, we examined the expression of activated c-Src in tissue sections from surgically resected human breast specimens. First, we confirmed the specificity of the antibody against activated c-Src (Clone 28) using six cell lines established from human breast carcinomas by western blotting. As expected, activated c-Src was detected as a 60 kDa band in all cell lines tested. Immunofluorescence analysis demonstrated that the activated c-Src was mainly observed in cytoplasms of these cells. Then, we designed an immunohistochemical study with 73 human breast carcinoma tissues. Glandular epithelial and myoepithelial cells in normal mammary glands adjacent to carcinoma nests and infiltrating **stromal cells** were negative for activated c-Src. In contrast, 37 of the 73 breast carcinoma tested (50.7%) were positive for activated c-Src, and this positive staining was inversely correlated with Ki-67 labeling index ($p < 0.0001$), TNM stage ($p < 0.0001$), tumor size ($p < 0.0001$), and histological grade ($p = 0.0002$). These results strongly suggest that the activation of c-Src would be related to the progression of breast carcinomas with low aggressiveness.

L6 ANSWER 29 OF 50 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:73697 SCISEARCH

THE GENUINE ARTICLE: 509KH
TITLE: Expression and localization of vascular endothelial growth factor-C in rheumatoid arthritis synovial tissue
AUTHOR: Wauke K; Nagashima M (Reprint); Ishiwata T; Asano G; Yoshino S
CORPORATE SOURCE: Nippon Med Coll, Dept Joint Dis & Rheumatism, Bunkyo Ku, 1-1-5 Sendagi, Tokyo 1138603, Japan (Reprint); Nippon Med Coll, Dept Joint Dis & Rheumatism, Bunkyo Ku, Tokyo 1138603, Japan; Nippon Med Coll, Dept Pathol, Bunkyo Ku, Tokyo 1138603, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: JOURNAL OF RHEUMATOLOGY, (JAN 2002) Vol. 29, No. 1, pp. 34-38.
Publisher: J RHEUMATOL PUBL CO, 920 YONGE ST, SUITE 115, TORONTO, ONTARIO M4W 3C7, CANADA.
ISSN: 0315-162X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 29

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective. Vascular endothelial growth factor-C (VEGF-C), a member of the VEGF family. induces lymphangiogenesis through VEGF receptor-3 (VEGFR-3/Flt-4). We examined the expression and localization of VEGF-C to clarify its role in synovial tissues in rheumatoid arthritis (RA).

Methods. Reverse transcription-polymerase chain reaction (RT-PCR), Western blot analysis, immunohistochemical staining, and in situ hybridization for VEGF-C were performed on synovial tissue specimens obtained from 10 patients with RA and 4 with osteoarthritis (OA), VEGFR-3 expression was determined using Western blot analysis.

Results. RT-PCR analysis showed that VEGF-C mRNA was expressed in all RA and OA synovial tissues. Based on Western blot analysis, the mature form of VEGF-C was round in RA synovial tissues, but not in OA synovial tissues, and VEGFR-3 was detected in RA and OA synovial tissues. Immunohistochemical staining showed that the VEGF-C protein was localized in many synovial lining cells, endothelial cells, and **stromal cells** in RA synovial tissues. In OA synovial tissues, the VEGF-C protein was localized in synovial lining cells and endothelial cells, A large number of synovial lining cells and **stromal cells** surrounding microvessels in RA synovial tissues expressed VEGF-C mRNA, as determined by in situ hybridization.

Conclusion. Mature VEGF-C and VEGFR-3 expression may contribute to lymphangiogenesis in RA.

L6 ANSWER 30 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:164949 BIOSIS
DOCUMENT NUMBER: PREV200300164949
TITLE: VEGFR-3 in Cornea Lymphangiogenesis and APC Trafficking.
AUTHOR(S): Chen, L. [Reprint Author]; Hamrah, P. [Reprint Author]; Zhang, Q. [Reprint Author]; Dana, M. R. [Reprint Author]
CORPORATE SOURCE: Department of Ophthalmology, Schepens Eye Research Institute, Harvard Medical School, Boston, MA, USA
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2268. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 2003
Last Updated on STN: 2 Apr 2003

AB Purpose: Previous data from this lab indicate that lymphatic flow from the cornea to draining **lymph nodes** (LN) plays an important

role in corneal immunity. Specifically, corneal transplantation to BALB/c hosts that had their cervical LN excised before surgery showed indefinitely and universal graft acceptance (Yamagami S. & Dana M.R., 2001). VEGFR-3 (Flt-4) is a receptor tyrosine **kinase** which is mainly expressed on the lymphatic endothelium in adult tissues. The purpose of this study is to elucidate the expressional changes of VEGFR-3 during corneal neovascularization (NV) and its possible roles in cornea lymphangiogenesis and APC trafficking. Methods: Corneal NV was induced by intrastromal 11-0 nylon sutures in Balb/c mice. Eyes were procured 1, 3, 7, 14 days after the manipulation. Lymphatic vessels and VEGFR-3 positive cells were identified by confocal microscopy with immunofluorescence staining. Results: Cornea lymphatic vessels were detected with VEGFR-3 and CD31 double staining in corneal whole mounts starting at day 3 during induction of corneal NV. Cross sectional studies additionally revealed that the ocular surface epithelium of normal eyes express high levels of VEGFR-3. A sharp increase in VEGFR-3 staining in the corneal stroma was observed during the first week after induction of NV and a transient increase of VEGFR-3 expression on the epithelial layers of the limbus and conjunctival region around day 3 was also found. Additionally, corneal inflammation was associated with enhanced expression of VEGFR-3 by CD11c+ corneal dendritic cells. Conclusion: The expression of VEGFR-3 in the cornea and ocular surface is modified during corneal NV, both at the level of lymphatic vessels, and epithelial and **stromal cells** . These changes may affect trafficking of antigens and/or antigen-presenting cells from the eye to lymphoid organs and provide one explanation for why eyes with NV are considered 'high-risk' candidates for allograft survival. Additional studies including the use of recombinant VEGFR-3 chimeric protein in allograft cornea transplantation were undertaken to further define the possible functional roles of this receptor in lymphatic drainage and graft survival. Support: NIH/NEI Grant EY12963.

L6 ANSWER 31 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:356767 BIOSIS
DOCUMENT NUMBER: PREV200300356767
TITLE: Loss of Function Mutations of PI3Kgamma or PLCbeta2/beta3 Impair T-Cell Migration to SDF.
AUTHOR(S): Bach, Tami L. [Reprint Author]; Huang, Minzhou [Reprint Author]; Wu, Dianqing [Reprint Author]; Zigmond, Sally H. [Reprint Author]; Abrams, Charles S. [Reprint Author]
CORPORATE SOURCE: Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 2633. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 18 Sep 2003

AB Leukocyte chemotaxis plays a role in both the immune and inflammatory response. **Stromal cell**-derived factor-1alpha (SDF-1alpha) is a member of the CXC chemokine subfamily that stimulates T lymphocytes via activation of a Galphai-coupled receptor. Studies with knockout mice have demonstrated a critical role for D3-phosphoinositide production by phosphatidylinositol 3-**kinase** gamma (PI3Kgamma) in Galphai-coupled receptor mediated neutrophil chemotaxis. Similar studies have failed to demonstrate a role for IP3 or DAG production by phospholipase Cbeta (PLCbeta) in this neutrophil response. The role of

phospholipid second messengers generated by PI3Kgamma or PLCbeta in lymphocyte chemotaxis is less well known. In the current investigation, murine T lymphocytes were studied to determine whether loss of function mutations within either PI3Kgamma, or both of the two dominant lymphocyte PLCbeta isoforms (PLCbeta2 & PLCbeta3), affected lymphocyte migration in response to SDF-1alpha. Using a transwell assay, peripheral T-cells were isolated from the **lymph nodes** of knockout and control mice. Migration from the top chamber into the bottom chamber after 3 hours was quantitated in the absence, or presence, of 37.5 nM SDF-1alpha in the lower chamber. Flow cytometry was used to quantitate the number of cells in each chamber. The lymphocytes isolated from control wild type mice exhibited a 2.5-4-fold increase in migration with SDF-1alpha stimulation compared to baseline. In contrast, loss of either PI3Kgamma or PLC beta2/beta3 decreased chemokine-stimulated cell migration by 29.0% +/- 5.5% ($p<0.05$) and 49.3% +/- 3.1% ($p<0.001$), respectively. Furthermore, inhibition of PI3K by either wortmannin (233 nM) or LY294002 (50 muM), completely eliminated SDF-1alpha-induced migration of either the wild type cells or cells lacking PI3Kgamma. This latter observation suggests that PI3K isoforms other than PI3Kgamma, also contribute to the chemotactic response. These results show that in vivo phospholipid second messenger formation by both PI3Kgamma and PLCbeta plays a critical role in lymphocyte chemotaxis. Our data demonstrate that although PLCbeta-mediated signaling plays no role in neutrophil chemotaxis, it makes a substantial contribution to this process within T-lymphocytes.

L6 ANSWER 32 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:836585 HCAPLUS
DOCUMENT NUMBER: 136:353325
TITLE: PIP92 and NVM-1: Two genes associated with motility and metastasis
AUTHOR(S): Novac, Natalia
CORPORATE SOURCE: Inst. Toxikologie Genetik, Univ. Karlsruhe, Germany
SOURCE: Wissenschaftliche Berichte - Forschungszentrum Karlsruhe (2001), FZKA 6655, A, B, i-iii, iv-xvii, 1-165
CODEN: WBFKF5; ISSN: 0947-8620
DOCUMENT TYPE: Report
LANGUAGE: English

AB The differential screening method of Suppression Subtractive Hybridization (SSH) has previously been used to compare/identify genes associated with tumor progression and metastasis. More than a hundred genes were up-regulated in the highly metastatic cell line ASML in comparison to its non-metastatic counterpart IAS cells. In her thesis work the author has further differentially screened this group of genes to identify those that might play a role in the migration of metastasizing cells. This was achieved by analyzing the expression of these genes in mobilized and resident macrophages and in activated and non-activated lymphocytes. Those genes identified by these screens were then further screened for metastasis-related expression in multiple tumor models. Following this screening, two genes were selected for further characterization, Pip92 and NVM-1. Pip92 belongs to the "immediate early" gene family and has not previously been associated with tumor progression and metastasis. Its function is still obscure. To permit the functional anal. of the Pip92 protein polyclonal antibodies were generated. Pip92 has previously been shown by others to be cytoplasmic. However, the results obtained in the authors' work suggest that the Pip92 protein translocates to the nuclei for example upon serum stimulation. To get an insight into the functional role of Pip92, the phenotype of IAS-Bsp73 cells stably overexpressing Pip92 protein was studied. IAS cells ectopically expressing the Pip92 protein exhibit enhanced motility in in vitro migration assays as compared to empty vector-transfected cells, suggesting that Pip92 might belong to the set of genes responsible for regulating cell migration. Properties of the Pip92 protein suggest it might act as a transcription regulatory protein and a search for genes whose expression is altered in

Pip92-overexpressing cells was therefore performed. The expression of three genes was clearly up-regulated in cells overexpressing Pip92. The strongest induction was observed for osteopontin, a gene whose expression has previously been associated with migration and metastasis. Sections of human tumors dissected from patients with invasive ductal carcinoma were immunostained with the Pip92 antiserum. Pos. staining was observed only in tumor cells but not in non-neoplastic healthy tissues. NVM-1 (novel gene associated with metastasis) is a previously undescribed gene. Its full-length coding sequence was isolated and the predicted open reading frame was confirmed by an in vitro transcription/translation. The correlation of expression of NVM-1 with metastasis was confirmed in three tumor progression models in addition to one used for SSH. Upon completion of the human genome sequencing project it became apparent that the human homolog of NVM-1 (hNVM-1) gene is located on chromosome 14. The predicted amino acid sequence of hNVM-1 shows high homol. to the rat sequence. The genome sequence allowed the author to characterize the hNVM-1 promoter and the gene structure. Anal. of the hNVM-1 promoter revealed a number of potential transcription factor-binding sites within the putative hNVM-I promoter sequence. The hNVM-1 gene consists of 6 exons and 5 introns. A thorough computer anal. of the hNVM-1 gene structure and ESTs revealed the presence of two splice donor sites at the exon 2-intron 2 junction which are alternatively used in different tissues of human and rodent origin. Monoclonal antibodies against rNVM-I protein were generated and proved to be useful for Western Blot and immunohistochem. analyses, demonstrating a cytoplasmic location for the rNVM-I protein and expression of the protein in tumors. Further study of these genes may lead to the discovery of the new targets for antitumor drugs and may significantly help us to understand the process of transformation of nonmetastatic tumor cells into metastatic ones.

REFERENCE COUNT: 296 THERE ARE 296 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 33 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:851435 HCAPLUS
DOCUMENT NUMBER: 136:1570
TITLE: Compositions, kits, and methods for identification and modulation of T helper-1 and T helper-2 cells and diseases associated therewith
INVENTOR(S): Hanrahan, Catherine F.; Feldman, Marc; Trepicchio, William L.
PATENT ASSIGNEE(S): Genetics Institute, Inc., USA; Kennedy Institute of Rheumatology
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001088199	A2	20011122	WO 2001-US16022	20010517
WO 2001088199	A3	20030206		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2409154	AA	20011122	CA 2001-2409154	20010517

US 2002039734 A1 20020404 US 2001-860655 20010517
EP 1299560 A2 20030409 EP 2001-933353 20010517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2000-205204P P 20000518
WO 2001-US16022 W 20010517

AB The invention relates to compns., kits and methods for identifying, detecting, and modulating the differentiation, growth, and/or maturation of Th1 or Th2 cells. The invention further relates to compns., kits, and methods for detecting, characterizing, preventing, and treating a Th1- or Th2-associated condition. A variety of markers are provided, wherein changes in the levels of expression of one or more of the markers is correlated with the presence of a Th1 or Th2 cell or Th1- or Th2-associated condition. Macrophage inhibitory factor (MIF) gene expression which is increased in both Th1-inducing and TH2-inducing condition is analyzed.

L6 ANSWER 34 OF 50 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:159721 SCISEARCH
THE GENUINE ARTICLE: 400HY
TITLE: Expression of the c-met proto-oncogene and its ligand, hepatocyte growth factor, in Hodgkin disease
AUTHOR: Teofili L; Di Febo A L; Pierconti F; Maggiano N; Bendandi M; Rutella S; Cingolani A; Di Renzo N; Musto P; Pileri S; Leone G; Larocca L M (Reprint)
CORPORATE SOURCE: Catholic Univ Sacred Heart, Inst Pathol, Largo F Vito 1, I-00168 Rome, Italy (Reprint); Catholic Univ Sacred Heart, Inst Pathol, I-00168 Rome, Italy; Catholic Univ Sacred Heart, Inst Hematol, I-00168 Rome, Italy; Catholic Univ Sacred Heart, Inst Infect Dis, I-00168 Rome, Italy; Casa Solievo Sofferenza, Div Hematol, Dept Onco Hematol, S Giovanni Rotondo, Italy; Univ Bologna, Inst Hematol Seragnoti, Bologna, Italy
COUNTRY OF AUTHOR: Italy
SOURCE: BLOOD, (15 FEB 2001) Vol. 97, No. 4, pp. 1063-1069. Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA. ISSN: 0006-4971.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 42

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The receptor for hepatocyte growth factor (HGF) is a transmembrane tyrosine **kinase** that is encoded by the proto-oncogene c-met Recently, c-MET was detected in Reed-Sternberg (RS) cells from Epstein-Barr virus-positive (EBV+) Hodgkin disease (HD). The c-MET, EBER-1, and LMP-1 expression in 45 **lymph node** biopsies and 12 bone marrow biopsies obtained from patients with HD was analyzed. In addition, HGF levels in serum samples from 80 healthy individuals and 135 HD patients in different phases of disease. In all 45 **lymph node** and 12 bone marrow samples examined, RS cells expressed c-MET but not HGF(+). These results were independent of the EBV infection. Interestingly, several HGF+ dendritic-reticulum cells were found scattered around c-MET+ RS cells. The mean a SEM serum HGF levels in HD patients at diagnosis and at the time of relapse were 1403 +/- 91 (95% confidence interval [CI], 1221-1585) and 1497 +/- 242 pg/mL (95% CI, 977-2017), respectively. HGF values were significantly higher than those of healthy individuals (665 +/- 28 pg/mL; 95% CI, 600-721; and $P < .001$ for both groups of patients) and of HD patients in remission (616 +/- 49 pg/mL; 95% CI, 517-714; and $P < .001$ for both groups of patients). A significant correlation was found between serum HGF levels and B symptoms at diagnosis ($P = .014$). In conclusion, this study indicates that HGF and c-MET constitute an additional signaling pathway between RS cells and the reactive cellular background, thereby affecting adhesion, proliferation,

and survival of RS cells. Furthermore, the serum concentration of HGF in HD patients may be a useful tool in monitoring the status of (C) 2001 by The American Society of Hematology.

L6 ANSWER 35 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2001429559 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11477575
TITLE: Clinicopathological significance of vascular endothelial growth factor (VEGF)-C in human esophageal squamous cell carcinomas.
AUTHOR: Kitadai Y; Amioka T; Haruma K; Tanaka S; Yoshihara M; Sumii K; Matsutani N; Yasui W; Chayama K
CORPORATE SOURCE: Department of Endoscopy, Hiroshima University School of Medicine, Hiroshima, Japan.. ykitadai@mcai.med.hiroshima-u.ac.jp
SOURCE: International journal of cancer. Journal international du cancer, (2001 Sep 1) 93 (5) 662-6.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816

AB The purpose of this study was to investigate the expression of vascular endothelial growth factor (VEGF) -C in human esophageal squamous cell carcinomas to elucidate its role in **lymph node** metastasis and tumor progression. The expression of VEGF-C and flt-4 genes was examined in 5 esophageal carcinoma cell lines, 12 fresh biopsy specimens and 48 archival surgical specimens of human esophageal carcinoma tissues by RT-PCR and immunohistochemistry. Immunohistochemistry using antibodies against CD34 (endothelial cell specific) was also carried out and microvessels were quantified by counting vessels in a 200x field in the most vascular area of the tumor. Of the 5 human esophageal carcinoma cell lines, 4 constitutively expressed VEGF-C mRNA. In 8 (66.7%) of 12 cases, VEGF-C mRNA was detected in only tumor tissues but not in normal mucosa by RT-PCR. There was a significant relationship between VEGF-C and flt-4 mRNA expression. Out of the 48 surgical specimens of esophageal carcinomas, 19 (39.6%) and 10 (20.8%) exhibited intense VEGF-C immunoreactivity in the cytoplasm of many cancer cells and the **stromal cells**, respectively. In contrast, Flt-4 was mainly expressed on the lymphatic endothelial cells. Normal and dysplastic esophageal squamous epithelium exhibited no or faint cytoplasmic staining of VEGF-C. VEGF-C expression correlated with depth of tumor invasion, tumor stage, venous invasion, lymphatic invasion and **lymph node** metastasis. Vessel count was significantly higher in the VEGF-C positive tumors than in the negative tumors. These results overall suggest that VEGF-C may play a role in tumor progression via lymphangiogenesis and angiogenesis in human esophageal carcinoma.

L6 ANSWER 36 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004522048 EMBASE
TITLE: The contribution of inherited factors to the clinicopathological features and behavior of breast cancer.
AUTHOR: Foulkes W.D.; Rosenblatt J.; Chappuis P.O.
CORPORATE SOURCE: W.D. Foulkes, Montreal General Hospital, 1650 Cedar Avenue, Montreal, Que. H3G 1A4, Canada. william.foulkes@mcgill.ca
SOURCE: Journal of Mammary Gland Biology and Neoplasia, (2001) 6/4 (453-465).
Refs: 99

ISSN: 1083-3021 CODEN: JMBNFU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This review is focused on genetic factors that may influence the development and/or appearance of breast cancer metastases. Over the last decade there have been significant advances in the understanding of genetic predisposition to breast cancer. The first breast cancer predisposing gene to be identified was TP53, and this was followed over the next 5 years by two more genes, BRCA1 and BRCA2, which from a population perspective are much more important than TP53. Other rarer genes have subsequently been identified, but the role of more common, less penetrant genes in breast cancer susceptibility remains unknown. Recent work has shown that breast cancers occurring in women carrying germ-line BRCA1 mutations tend to have clinicopathological features that are usually associated with a poor prognosis, such as high grade, estrogen receptor negative status and somatic TP53 mutations. On the other hand, they are usually ERBB2 negative. Whether or not such tumors are more or less likely to metastasize, and hence be associated with a poor outcome, is currently uncertain and has been the subject of much debate. Here, we outline some of the clinicopathological features of hereditary breast cancer, discuss the prognostic studies that have been performed, and introduce some possible new research directions. .COPYRGT. 2002 Plenum Publishing Corporation.

L6 ANSWER 37 OF 50 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2001357671 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11418238
TITLE: Identification of a new fibroblast growth factor receptor, FGFR5.
AUTHOR: Sleeman M; Fraser J; McDonald M; Yuan S; White D; Grandison P; Kumble K; Watson J D; Murison J G
CORPORATE SOURCE: Genesis Research and Development Corporation Ltd., 1 Fox Street, Parnell, Auckland, New Zealand.
SOURCE: Gene, (2001 Jun 27) 271 (2) 171-82.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF321300; GENBANK-AF321301
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010827
Entered Medline: 20010823
AB A novel fibroblast growth factor receptor (FGFR), designated FGFR5, was identified from an EST database of a murine **lymph node stromal cell** cDNA library. The EST has approximately 32% identity to the extracellular domain of FGFR1-4. Library screening with this EST identified two full-length alternative transcripts which we designated as FGFR5 beta and FGFR5 gamma. The main difference between these transcripts is that FGFR5 beta contains three extracellular Ig domains whereas FGFR5 gamma contains only two. A unique feature of FGFR5 is that it does not contain an intracellular tyrosine **kinase** domain. Predictive structural modelling of the extracellular domain of FGFR5 gamma suggested that it was a member of the I-set subgroup of the Ig-superfamily, consistent with the known FGFRs. Northern analysis of

mouse and human FGFR5 showed detectable mRNA in a broad range of tissues, including kidney, brain and lung. Genomic sequencing identified four introns but identified no alternative transcripts containing a tyrosine **kinase** domain. Extracellular regions of FGFR5 beta and 5 gamma were cloned in-frame with the Fc fragment of human IgG(1) to generate recombinant non-membrane bound protein. Recombinant FGFR5 beta Fc and R5 gamma Fc demonstrated specific binding to the ligand FGF-2, but not FGF-7 or EGF. However, biological data suggest that FGF-2 binding to these proteins is with lower affinity than its cognate receptor FGFR2C. The above data indicate that this receptor should be considered as the fifth member of the FGFR family.

L6 ANSWER 38 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:861815 HCAPLUS
DOCUMENT NUMBER: 134:26116
TITLE: Protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor
INVENTOR(S): Bird, Timothy A.; Virca, G. Duke; Martin, Unja; Anderson, Dirk M.
PATENT ASSIGNEE(S): Immunex Corporation, USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073468	A1	20001207	WO 2000-US14696	20000526
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2374612	AA	20001207	CA 2000-2374612	20000526
EP 1181374	A1	20020227	EP 2000-939378	20000526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6514719	B1	20030204	US 2000-579664	20000526
US 2003162277	A1	20030828	US 2003-355975	20030130
US 6759223	B2	20040706		

PRIORITY APPLN. INFO.:
US 1999-136781P P 19990528
US 2000-579664 A3 20000526
WO 2000-US14696 W 20000526

AB The invention is directed to purified and isolated novel murine and human **kinase** polypeptides, the nucleic acids encoding such polypeptides, processes for production of recombinant forms of such polypeptides, antibodies generated against these polypeptides, fragmented peptides derived from these polypeptides, and the uses of the above. Protein and cDNA sequences of novel human mouse protein **kinase** sequence homologs are identified by querying sequence data bases with DNA sequences from murine dendritic cell, murine **lymph node stromal cell**, human dendritic cell and human spleen cDNA library, using an algorithm designed to recognize **kinase** subdomains. The invention further relates to methods for identifying novel **kinase** inhibitor.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 39 OF 50 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1999113739 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9916701
TITLE: Galectin-1 specifically modulates TCR signals to enhance TCR apoptosis but inhibit IL-2 production and proliferation.
AUTHOR: Vespa G N; Lewis L A; Kozak K R; Moran M; Nguyen J T; Baum L G; Miceli M C
CORPORATE SOURCE: Department of Microbiology and Immunology, University of California, Los Angeles, School of Medicine, 90095, USA.
CONTRACT NUMBER: CA-16042 (NCI)
R29 CA65979-01 (NCI)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1999 Jan 15) 162 (2) 799-806.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990208

AB Galectin-1 is an endogenous lectin expressed by thymic and **lymph node stromal cells** at sites of Ag presentation and T cell death during normal development. It is known to have immunomodulatory activity in vivo and can induce apoptosis in thymocytes and activated T cells (1-3). Here we demonstrate that galectin-1 stimulation cooperates with TCR engagement to induce apoptosis, but antagonizes TCR-induced IL-2 production and proliferation in a murine T cell hybridoma and freshly isolated mouse thymocytes, respectively. Although CD4+ CD8+ double positive cells are the primary thymic subpopulation susceptible to galectin-1 treatment alone, concomitant CD3 engagement and galectin-1 stimulation broaden susceptible thymocyte subpopulations to include a subset of each CD4- CD8-, CD4+ CD8+, CD4- CD8+, and CD4+ CD8- subpopulations. Furthermore, CD3 engagement cooperates with suboptimal galectin-1 stimulation to enhance cell death in the CD4+ CD8+ subpopulation. Galectin-1 stimulation is shown to synergize with TCR engagement to dramatically and specifically enhance extracellular signal-regulated **kinase**-2 (ERK-2) activation, though it does not uniformly enhance TCR-induced tyrosine phosphorylation. Unlike TCR-induced IL-2 production, TCR/galectin-1-induced apoptosis is not modulated by the expression of **kinase** inactive or constitutively activated Lck. These data support a role for galectin-1 as a potent modulator of TCR signals and functions and indicate that individual TCR-induced signals can be independently modulated to specifically affect distinct TCR functions.

L6 ANSWER 40 OF 50 MEDLINE on STN
ACCESSION NUMBER: 1999341447 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10414497
TITLE: The expression of basic fibroblast growth factor (bFGF) in tumor-associated **stromal cells** and vessels is inversely correlated with non-small cell lung cancer progression.
AUTHOR: Guddo F; Fontanini G; Reina C; Vignola A M; Angeletti A; Bonsignore G
CORPORATE SOURCE: Institute of Lung Pathophysiology, National Research Council, Palermo, Italy.
SOURCE: Human pathology, (1999 Jul) 30 (7) 788-94.
Journal code: 9421547. ISSN: 0046-8177.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303
Entered Medline: 19990803

AB Tumor progression results from complex interactions between tumor and tumor-associated host tissue. Basic fibroblast growth factor (bFGF), via activation of its receptor, FGFR-1, has been postulated to be an important inducer of host stromal response and angiogenesis. To assess the putative role of tumor-associated **stromal cells** and vessels in tumor progression, we studied non-small cell lung cancer (NSCLC) from 84 patients, including 51 squamous cell carcinomas and 33 nonsquamous cell carcinomas, by immunohistochemical detection. bFGF and FGFR-1 immunoreactivity was observed in tumor and in tumor-associated **stromal cells** and vessels. The expression of bFGF and FGFR-1 in **stromal cells** was higher in squamous than in non-squamous cell carcinomas (respectively, P = .007 and P = .0004). We found that bFGF and FGFR-1 expression in tumor and tumor-associated **stromal cells** and vessels was directly correlated with host stromal response, as assessed by intratumoral extension of stroma, but not with angiogenic response, as assessed by microvessel count. Although FGFR-1 expression of tumor cells was directly correlated with T-stage (P = .03), bFGF expressions of tumor-associated **stromal cells** and vessels were inversely correlated with **lymph node** metastasis (respectively, P = .0001 and P = .0002) and advanced pathological stage (respectively, P = .03 and P = .01). These findings suggest that bFGF might mediate host stromal response in NSCLC and that the expression of bFGF in tumor-associated **stromal cells** and vessels might have an inhibitory role in NSCLC progression.

L6 ANSWER 41 OF 50 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:546891 SCISEARCH
THE GENUINE ARTICLE: ZZ446
TITLE: Binding of human immunodeficiency virus type 1 to CD4 and CXCR4 receptors differentially regulates expression of inflammatory genes and activates the MEK/ERK signaling pathway
AUTHOR: Popik W; Hesselgesser J E; Pitha P M (Reprint)
CORPORATE SOURCE: JOHNS HOPKINS UNIV, SCH MED, CTR ONCOL, 418 N BOND ST, BALTIMORE, MD 21231 (Reprint); JOHNS HOPKINS UNIV, SCH MED, CTR ONCOL, BALTIMORE, MD 21231; JOHNS HOPKINS UNIV, SCH MED, DEPT MOL & GENET, BALTIMORE, MD 21231; BERLEX BIOSCI, DEPT IMMUNOL, RICHMOND, CA 94804
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF VIROLOGY, (AUG 1998) Vol. 72, No. 8, pp. 6406-6413.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0022-538X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 60

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have previously shown that binding of human immunodeficiency virus type 1 (HIV-1) virions to CD4 receptors stimulates association of Lck with Raf-1 and results in the activation of Raf-1 **kinase** in a Ras-independent manner. In the present study, we demonstrate that HIV-1 envelope glycoproteins of both T-cell-tropic and macrophagetropic strains rapidly activate the ERK/mitogen-activated protein (MAP) **kinase** pathway and the binding of nuclear transcription factors (AP-1, NF-kappa

B, and C/EBP) and stimulate expression of cytokine and chemokine genes. The activation of this signaling pathway requires functional CD4 receptors and is independent of binding to CXCR4. Binding of the natural ligand **stromal cell**-derived factor 1 (SDF-1) to CXCR4, which inhibits entry of T-cell-tropic HIV-1, activates also the ERK/MAP **kinase** pathway. Bow ever, SDF-1 did not affect the CD4-mediated expression of cytokine and chemokine genes. These results provide firm molecular evidence that binding of HIV-1 envelope glycoproteins to CD4 receptor initiates a signaling pathway(s) independent of the binding to the chemokine receptor that leads to the aberrant expression of inflammatory genes and may contribute significantly to HIV-1 replication as well as to deregulation of the immune system.

L6 ANSWER 42 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:776422 HCAPLUS
DOCUMENT NUMBER: 130:166834
TITLE: Regulation of adhesion and migration in the germinal center microenvironment
AUTHOR(S): Pals, Steven T.; Taher, Taher E. I.; Van Der Voort, Robbert; Smit, Lia; Keehnen, Robert M. J.
CORPORATE SOURCE: Department of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, 1105 AZ, Neth.
SOURCE: Cell Adhesion and Communication (1998), 6(2-3), 111-116
CODEN: CADCEF; ISSN: 1061-5385
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 67 refs. T cell dependent humoral immune responses are initiated by the activation of naive B cells in the T cell areas of the secondary lymphoid tissues. This primary B cell activation leads to migration of germinal center (GC) cell precursors into B cell follicles where they engage follicular dendritic cells (FDC) and T cells, and differentiate into memory B cells or plasma cells. Both B cell homing to the GC and interaction with FDC critically depend on integrin-mediated adhesion. We have recently identified the c-met-encoded receptor tyrosine **kinase** and its ligand, the growth and motility factor hepatocyte growth factor/scatter factor (HGF/SF), as a novel paracrine signaling pathway regulating B cell adhesion. The c-Met protein is expressed on B cells localized in the dark zone of the GC (centroblasts) and is induced by CD40 plus BCR ligation. Stimulation of c-Met with HGF/SF, which is produced at high levels by tonsillar **stromal cells** and FDC, leads to receptor phosphorylation and to enhanced integrin-mediated adhesion of B cells to both VCAM-1 and fibronectin. Interestingly, these responses to HGF/SF are promoted by heparan-sulfate proteoglycan forms of CD44 (CD44-HS). Like c-Met, CD44-HS is induced on B cells by CD40 ligation. It efficiently binds HGF/SF and strongly promotes signaling through c-Met. We conclude that integrin regulation during antigen specific B cell differentiation involves cross-talk between the HGF/SF-c-Met pathway and CD44-HS.
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 43 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998113479 EMBASE
TITLE: Characteristics of the conditioned medium produced by CA-12 **lymph node stromal cells**.
AUTHOR: Lee S.-H.; Lee D.-S.; Seu Y.-B.; Kim J.-G.; Tsuruo T.; Hong S.-D.
CORPORATE SOURCE: S.-D. Hong, Department of Microbiology, Kyungpook National University, Taegu 702-701, Korea, Republic of. leesh@rockvex.rockefeller.edu

SOURCE: Journal of Microbiology and Biotechnology, (1998) 8/1 (74-80).
Refs: 21
ISSN: 1017-7825 CODEN: JOMBES
COUNTRY: Korea, Republic of
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB CS-21 lymphoma cells that preferentially metastasize to **lymph nodes** after s.c. inoculation into BALB/c mice were grown in vitro in the presence of CA-12 **stromal cells** isolated from **lymph nodes**. In order to obtain fundamental data on the identification and characterization of the soluble factors produced by CA-12 **stromal cells**, the conditioned medium of CA-12 **stromal cells** that inhibited apoptosis of CS-21 cells was examined. Various analytical treatments revealed that the soluble factors in CA-12 conditioned medium are very sensitive to heat treatment and trypsinization. Moreover CA- 12 conditioned medium has an affinity with heparin but not with Con-A. In addition to these, the activity of CA-12 conditioned medium was blocked by H- 7, a PKC inhibitor, but the conditioned medium could not induce the differentiation of thymocytes. We concluded that CA-12 conditioned medium contains **stromal cell**-derived apoptosis-inhibitory molecules that play an important role in proliferation of CS-21 cells by suppressing cell apoptosis.

L6 ANSWER 44 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:403715 HCAPLUS
DOCUMENT NUMBER: 127:134638
TITLE: Paracrine regulation of germinal center B cell adhesion through the c-Met-hepatocyte growth factor/scatter factor pathway
AUTHOR(S): van der Voort, Robbert; Taher, Taher E. I.; Keehnen, Robert M. J.; Smit, Lia; Groenink, Martijn; Pals, Steven T.
CORPORATE SOURCE: Dep. Pathology, Academic Med. Center, Univ. Amsterdam, Amsterdam, Neth.
SOURCE: Journal of Experimental Medicine (1997), 185(12), 2121-2131
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB T cell-dependent humoral immune responses are initiated by the activation of naive B cells in the T cell areas of the secondary lymphoid tissues. This primary B cell activation leads to migration of germinal center (GC) cell precursors into B cell follicles where they engage follicular dendritic cells (FDC) and T cells, and differentiate into memory B cells or plasma cells. Both B cell migration and interaction with FDC critically depend on integrin-mediated adhesion. To date, the physiol. regulators of this adhesion were unknown. Here, the authors have identified the c-met-encoded receptor tyrosine **kinase** and its ligand, the growth and motility factor hepatocyte growth factor/scatter factor (HGF/SF), as a novel paracrine signaling pathway regulating B cell adhesion. The authors observed that c-Met is predominantly expressed on CD38+CD77+ tonsillar B cells localized in the dark zone of the GC (centroblasts). On tonsil B cells, ligation of CD40 by CD40-ligand, induces a transient strong upregulation of expression of the c-Met tyrosine **kinase**. Stimulation of c-Met with HGF/SF leads to receptor phosphorylation and, in addition, to enhanced integrin-mediated adhesion of B cells to both VCAM-1 and fibronectin. Importantly, the

c-Met ligand HGF/SF is produced at high levels by tonsillar **stromal cells** thus providing signals for the regulation of adhesion and migration within the lymphoid microenvironment.

L6 ANSWER 45 OF 50 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1998098359 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9436028
TITLE: Human prostate cancer progression models and therapeutic intervention.
AUTHOR: Chung L W; Kao C; Sikes R A; Zhau H E
CORPORATE SOURCE: Department of Urology, University of Virginia Health Sciences Center, Charlottesville, USA.
CONTRACT NUMBER: RO1 CA64863 (NCI)
SOURCE: Hinyokika kiyo. Acta urologica Japonica, (1997 Nov) 43 (11) 815-20. Ref: 12
Journal code: 0421145. ISSN: 0018-1994.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980224

AB Our laboratory has developed two cellular models of human prostate cancer progression. The LNCaP prostate cancer progression model is based upon the well-known cellular interaction between human prostate or bone **stromal cells** and LNCaP cells in vivo. The marginally tumorigenic LNCaP cells acquired tumorigenic and metastatic potential upon cellular interaction with either prostate or bone fibroblasts. A subline termed C4-2 was observed to grow readily in castrated animals and acquired metastatic potential spreading from the primary tumor site to the **lymph node**, the seminal vesicles, and the axial skeleton, resulting in an intense osteoblastic reaction. The second model is ARCaP, where prostate cancer cells derived from the ascites fluid of a man with metastatic disease exhibited an Androgen- and estrogen-Repressed Prostate Cancer cell growth and tumor formation in either a hormone-deficient or a castrated environment. However, the growth of either the tumor cells in vitro or the tumors in vivo was suppressed by both estrogen and androgen. While the tumor cells expressed low levels of androgen receptor and prostate-specific antigen (PSA), they were highly metastatic when inoculated orthotopically. Distant metastases to a number of organs were detected, including the liver, lung, kidney, and bone. We have employed a human prostate cancer progression model as a system to study the efficacy of gene therapy. Results of the study show that whereas universal promoters, such as Cytomegalovirus (CMV) and Rous Sarcoma Virus (RSV) promoter-driven tumor suppressors (e.g. p53, p21, and p16), were effective in inhibiting prostate tumor growth, the advantages of driving the expression of therapeutic toxic genes using a tissue-specific promoter prostate-specific antigen (PSA) and a tumor--but not tissue-specific promoter, osteocalcin (OC), are preferred. In the case of the PSA promoter, we can achieve cell-kill in PSA-producing human prostate cancer cells. To circumvent the supporting role of bone stroma for prostate cancer epithelial growth, we have recently developed a novel concept where the expression of therapeutic toxic genes is driven by a tumor--but not a tissue-specific OC promoter. Osteocalcin-thymidine **kinase** (OC-TK) was found to efficiently eradicate the growth of osteosarcoma, prostate, and brain tumors both in vitro and in vivo. We observed that androgen-independent human prostate cancer cells lines expressed OC-TK at higher levels than androgen-dependent human prostate cancer cell lines. We have obtained data to suggest that Ad-OC-TK plus a pro-drug acyclovir (ACV) may be used as an effective therapy to treat

prostate cancer bone metastasis in models where the growth of androgen-independent PC-3 and C4-2 tumors in the bone has occurred.

L6 ANSWER 46 OF 50 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 97122514 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8968108
TITLE: Induction of fibroblast gelatinase B expression by direct contact with cell lines derived from primary tumor but not from metastases.
AUTHOR: Segain J P; Harb J; Gregoire M; Meflah K; Menanteau J
CORPORATE SOURCE: Unite Institut National de la Sante et de la Recherche Medicale U 419,Institut de Biologie, Centre Hospitalier Universitaire, Nantes, France.
SOURCE: Cancer research, (1996 Dec 1) 56 (23) 5506-12. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 20000303
Entered Medline: 19970124
AB During cancer progression, tumor cells interact with **stromal cells**. As a consequence, matrix metalloproteinases are produced that contribute to the degradation of the extracellular matrix. This study used coculture systems to investigate fibroblast interaction with three colon cancer cell lines isolated from a single patient. Cells from primary colorectal carcinoma, but not from corresponding liver or **lymph node** metastases, induced gelatinase B expression by fibroblasts of different tissue origin. Remarkably, direct cell-cell contact was required for this induction, which occurred at the pretranslational level (as revealed by Northern blot analysis) and was completely blocked by anti-beta1 integrin monoclonal antibody, but only partially blocked by anti-alpha5 or anti-alpha(v). Induction was also inhibited by cytochalasin D, staurosporine, or dexamethasone, suggesting the need, respectively, for an organized actin cytoskeleton, protein **kinase** C, and AP-1-driven gene transcription. Our data suggest that direct tumor-**stromal cell** contact is one inductive event involved in matrix metalloproteinase expression by **stromal cells**.

L6 ANSWER 47 OF 50 EMBASE
on STN DUPLICATE 14
ACCESSION NUMBER: 95155187 EMBASE
DOCUMENT NUMBER: 1995155187
TITLE: Involvement of CD45 in adhesion and suppression of apoptosis of mouse malignant T-lymphoma cells.
AUTHOR: Hanaoka K.; Fujita N.; Lee S.-H.; Seimiya H.; Naito M.; Tsuruo T.
CORPORATE SOURCE: Laboratory of Biomedical Research, Molecular/Cellular Biosciences Inst., University of Tokyo, 1-1-1, Yayoi,Bunkyo-ku, Tokyo 113, United States
SOURCE: Cancer Research, (1995) 55/10 (2186-2190). ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Mouse malignant T-lymphoma CS-21 cells undergo apoptotic cell death in vitro in the absence of **lymph node stromal cells** but escape apoptosis and proliferate when they are attached

to CA-12 **stromal cells**. A monoclonal antibody raised against CS-21 cell surface molecules (MCS-5) recognized a M(r) 168,000 protein, inhibited binding of CS-21 cells to CA-12 **stromal cells**, and suppressed apoptosis in CS-21 cells. To identify the M(r) 168,000 protein, we purified it with MCS-5 affinity chromatography and ion exchange chromatography. Partial amino acid sequences of the purified M(r) 168,000 protein were identical to those of CD45, a transmembrane tyrosine phosphatase. The purified protein possessed tyrosine phosphatase activity and was recognized by an anti-CD45 monoclonal antibody. The M(r) 168,000 protein was identified as CD45. To determine the CD45 isoform, we cloned the CD45 gene from the cDNA library of CS-21. Sixteen or 18 clones encoded CD45RO (CD45 lacking exons 4, 5, and 6), and the remainder lacked exons 4, 5, 6, and 7. Like MCS-5, an anti-CD45 monoclonal antibody, also inhibited binding of CS-21 cells to CA-12 cells and suppressed apoptosis in CS-21 cells. Our present results indicate that CD45RO expressed un CS-21 cells mediates adhesion to CA-12 cells and suppression of apoptosis.

L6 ANSWER 48 OF 50 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:491699 HCAPLUS
DOCUMENT NUMBER: 122:236647
TITLE: Apoptosis inhibition by anti-Mr 23,000 (Thy-1) monoclonal antibodies without inducing bcl-2 expression
AUTHOR(S): Fujita, Naoya; Naito, Mikihiko; Lee, Sang-Han; Hanaoka, Kenji; Tsuruo, Takashi
CORPORATE SOURCE: Inst. Molecular Cellular Biosciences, Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Cell Growth & Differentiation (1995), 6(4), 355-62
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mouse malignant T-lymphoma CS-21 cells grow in vitro in the presence of CA-12 **stromal cells**, but they undergo apoptotic cell death with DNA fragmentation when cultured alone. Because apoptosis of CS-21 cells was not inhibited by soluble factors secreted from CA-12 **stromal cells**, cell-cell interactions between the two seemed to be important to inhibit apoptosis. The authors found that CS-21 cell adhesion was mediated by Mr 168,000 and Mr 23,000 proteins and that apoptosis-inhibitory signals were transmitted through these proteins. In this study, the authors identified the Mr 23,000 cell adhesion mol. as a glycosylphosphatidylinositol-anchored Thy-1 (CD90) glycoprotein. Crosslinking of Mr 23,000 protein with anti-Mr 23,000 mAb and a second antibody transiently raised the [Ca2+]i and activated calcineurin in CS-21 cells, as has been observed in normal T lymphocytes stimulated by crosslinking anti-Thy-1 mAbs. However, differing from normal T lymphocytes, CS-21 cells could grow either by the transient increase in [Ca2+]i or by the activation of protein **kinase** C. Furthermore, Mr 23,000 protein-mediated cell survival of CS-21 cells was not accompanied by expression of the apoptosis-inhibiting protein bcl-2, although protein **kinase** C-activated cell survival was attended by bcl-2 expression. These results indicate that the Mr 23,000 protein (Thy-1) of CS 21 lymphoma cells functions as a cell adhesion mol. capable of transducing signals of cell survival and growth that are not followed by bcl-2 expression.

L6 ANSWER 49 OF 50 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 95295089 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7539865
TITLE: c-met proto-oncogene expression in benign and malignant human prostate tissues.
AUTHOR: Pisters L L; Troncoso P; Zhau H E; Li W; von Eschenbach A C; Chung L W

CORPORATE SOURCE: Department of Urology, University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.
CONTRACT NUMBER: R01-CA56307 (NCI)
R01-CA57361 (NCI)
R01-CA64863 (NCI)
+
SOURCE: Journal of urology, (1995 Jul) 154 (1) 293-8.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 20000303
Entered Medline: 19950707

AB Previously, we demonstrated that hepatocyte growth factor/scatter factor (HGF/SF) is expressed by human bone **stromal cells** and is a powerful mitogen to prostatic epithelial cells in culture. Based on these observations, we hypothesized that, if prostate cancer cells in the prostate or bone environment respond to HGF/SF as a mitogen, then they must express the HGF/SF receptor, which is coded by the c-met proto-oncogene. We used immunohistochemical techniques to: 1) assess the presence and localization of c-met protein in benign and malignant human prostate tissues and 2) correlate the presence of c-met protein with tumor stage, grade and androgen sensitivity. c-met protein immunostaining was consistently observed in the basal epithelial layer of normal prostate glands but was absent in luminal epithelial cells of the peripheral and transition zones. c-met protein immunostaining was detected in 10 of 11 foci (91%) of high grade prostatic intraepithelial neoplasia (PIN). Overall, c-met protein staining was noted in 36 of 43 (84%) primary prostate cancer samples versus 2 of 11 (18%) benign prostate hyperplasia samples ($p < 0.0001$) and in 4 of 4 (100%) **lymph node** metastases, 23 of 23 (100%) bone marrow metastases and 1 of 3 (33%) other metastatic sites. There was a clear relationship between c-met protein staining and higher grade adenocarcinomas ($p < 0.001$). c-met protein is frequently detected in PIN and higher grade prostate cancers; future studies should evaluate the biological significance of these findings.

L6 ANSWER 50 OF 50 MEDLINE on STN
ACCESSION NUMBER: 95331136 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7607087
TITLE: Developmental expression of the mouse c-rel proto-oncogene in hematopoietic organs.
AUTHOR: Carrasco D; Weih F; Bravo R
CORPORATE SOURCE: Department of Molecular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.
SOURCE: Development (Cambridge, England), (1994 Oct) 120 (10) 2991-3004.
Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950828
Last Updated on STN: 20000303
Entered Medline: 19950814

AB We have studied the expression of the c-rel proto-oncogene during mouse embryonic development and adult animals using in situ hybridization and immunocytochemical analysis. c-rel transcripts were detected late in development with an expression pattern that parallels the emergence and diversification of hematopoietic cells. In the embryo, c-rel is expressed

first in the mesoderm-derived hematopoietic cells of the liver and later also in other hematopoietic tissues such as thymus and spleen. This correlation between c-rel expression and places of hematopoietic infiltration is conserved in the postnatal period, with expression of c-rel mRNA in the medullary region of the thymus and in splenic B cell areas, including the marginal zone and the outer region of the periarterial sheath. High levels of c-rel transcripts were also detected in the splenic germinal centers, **lymph nodes** and Peyer's patches. Using double immunofluorescence and cell preparations from different embryonic and adult hematopoietic organs, we have defined the pattern and cell types of c-rel expression in different hematopoietic cell lineages and in the **stromal cell** content of the thymus. By using electrophoretic mobility shift assays, we have also correlated c-Rel expression in spleen with kappa B-binding activity in the form of c-Rel/p50 and c-Rel/p52 heterodimers. The timing and pattern of expression of the c-rel proto-oncogene in the different cell lineages suggest that temporally regulated changes in c-Rel expression may be required for vertebrate hematopoiesis.

```
=> d his

     (FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1       1280537 S KINASE?
L2        385991 S LYMPH(A)NODE?
L3         65436 S STROMAL(W)CELL
L4          5129 S L1 AND L2
L5            92 S L3 AND L4
L6            50 DUP REM L5 (42 DUPLICATES REMOVED)

=> s l3(w)l2(w)l1
L7             0 L3(W) L2(W) L1

=> s l1(2w)l2
L8            15 L1(2W) L2

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9            13 DUP REM L8 (2 DUPLICATES REMOVED)

=> d 1-13 ibib ab

L9   ANSWER 1 OF 13  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:1142621  HCAPLUS
TITLE:                    Acquisition of lymph node, but not distant metastatic
                          potentials, by the overexpression of CXCR4 in human
                          oral squamous cell carcinoma
AUTHOR(S):                Uchida, Daisuke; Begum, Nasima-Mila; Tomizuka,
                          Yoshifumi; Bando, Takashi; Almofti, Ammar; Yoshida,
                          Hideo; Sato, Mitsunobu
CORPORATE SOURCE:         Second Department of Oral and Maxillofacial Surgery,
                          Tokushima University School of Dentistry, Kuramoto,
                          Tokushima, Japan
SOURCE:                   Laboratory Investigation (2004), 84(12), 1538-1546
                          CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER:                Nature Publishing Group
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Recently, it has been suggested that chemokine/receptor interactions determine
     the destination of the invasive tumor cells in several types of cancer.
     It has also been proposed that the stromal cell-derived factor-1 (SDF-1;
```

CXCL12)/CXCR4 system might be involved in lymph node metastasis in oral squamous cell carcinoma (SCC). To further clarify the role of the SDF-1/CXCR4 system in oral SCC, the authors generated CXCR4 stable transfectants (IH-CXCR4) using oral SCC cells, and compared them to IH, which did not express CXCR4 and which did not have lymph node metastatic potentials in vivo. The authors introduced enhanced green fluorescent protein (GFP) fused-CXCR4 into IH cells, and detected the GFP fluorescence in the cytoplasm and cell membrane in approx. 60% of the G418-resistant cells. This bulk-transfectant expressed a high level of CXCR4 mRNA and protein, and exhibited the characteristic calcium fluxes and chemotactic activity observed in treatment with SDF-1. SDF-1 biphasically activated extracellular signal-regulated kinase (ERK)1/2, but continuously activated Akt/protein kinase B (PKB) in IH-CXCR4 cells. Most importantly, IH-CXCR4 cells frequently metastasized to the cervical lymph node, but not to the distant organs in the orthotopic inoculation of nude mice. Furthermore, these lymph node metastases were inhibited by the treatment of a mitogen-activated protein kinase/ERK kinase inhibitor, U0126, or a phosphatidylinositol 3 kinase inhibitor, wortmannin. These results indicate that SDF-1/CXCR4 signaling mediates the establishment of lymph node metastasis in oral SCC via ERK1/2 or Akt/PKB pathway.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:866553 HCAPLUS

DOCUMENT NUMBER: 140:210093

TITLE: Gefitinib ('Iressa'), an epidermal growth factor receptor tyrosine kinase inhibitor, mediates the inhibition of lymph node metastasis in oral cancer cells

AUTHOR(S): Shintani, Satoru; Li, Chunnan; Mihara, Mariko; Nakashiro, Koh-ichi; Hamakawa, Hiroyuki

CORPORATE SOURCE: Department of Oral and Maxillofacial Surgery, Ehime University School of Medicine, Onsen-gun, Ehime, 791-0295, Japan

SOURCE: Cancer Letters (Oxford, United Kingdom) (2003), 201(2), 149-155
CODEN: CALEDQ; ISSN: 0304-3835

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB High expression of epidermal growth factor receptor (EGFR) is frequently observed in many solid tumor types including oral squamous cell carcinomas (OSCC). This study investigated whether treatment with gefitinib (Iressa), an EGFR-tyrosine kinase inhibitor, would inhibit the metastatic spread in OSCC cells. This was evaluated using orthotopic xenografts of highly metastatic OSCC. Metastasis was observed in six of 13 gefitinib treated animals (46.2%), compared with all of 12 control animals (100%). After exposure to gefitinib, OSCC cells showed a marked reduction in cell adhesion ability to fibronectin and in the expression of integrin α3, αv, β1, β4, β5 and β6.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:758933 HCAPLUS

DOCUMENT NUMBER: 138:167637

TITLE: Comparative Detection of Lymph Node Micrometastases of Stage II Colorectal Cancer by Reverse Transcriptase Polymerase Chain Reaction and Immunohistochemistry

AUTHOR(S): Noura, Shingo; Yamamoto, Hirofumi; Ohnishi, Tadashi; Masuda, Norikazu; Matsumoto, Takashi; Takayama, Osamu; Fukunaga, Hiroki; Miyake, Yasuhiro; Ikenaga, Masakazu; Ikeda, Masataka; Sekimoto, Mitsugu; Matsuura, Nariaki;

Monden, Morito
CORPORATE SOURCE: Department of Surgery and Clinical Oncology, Graduate Sch. Med., Osaka Univ., Osaka, Japan
SOURCE: Journal of Clinical Oncology (2002), 20(20), 4232-4241
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inconsistent conclusions were drawn about the clin. significance of micrometastases in lymph nodes (LNs) of node-neg. colorectal cancer (CRC) patients. We performed a comparative study of detection of micrometastases using immunohistochem. (IHC) by anti-cytokeratin antibody and carcinoembryonic antigen (CEA)-specific reverse-transcriptase PCR (RT-PCR) in the same patients, in an attempt to move closer to their clin. application. Sixty-four CRC patients, with RNA of good quality available from paraffin-embedded LN specimens, were selected from 84 stage II patients who underwent curative surgery between 1988 and 1996. We investigated assocns. between the presence of micrometastases by each method and prognosis. Micrometastases were detected in 19 (29.6%) of 64 patients by RT-PCR and in 35 (54.7%) of 64 patients by IHC. By RT-PCR anal., patients exhibiting a pos. band for CEA mRNA had a significantly worse prognosis than those who were RT-PCR-neg., with respect to both disease-free and overall survival (P = .027 and .015, resp.). By IHC anal., the presence of micrometastasis did not predict patient outcome in terms of either disease-free or overall survival. Infiltrating pattern of tumor growth characteristic was significantly associated with shorter disease-free survival among various clin. or pathol. factors. By multivariate Cox regression anal., micrometastasis detected by RT-PCR and the Crohn's-like lymphoid reaction were both independent prognostic factors. Micrometastases detected by RT-PCR, but not IHC, may be of clin. value in identifying patients who may be at high risk for recurrence of CRC and who are therefore likely to benefit from systemic adjuvant therapy.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:476563 HCAPLUS
DOCUMENT NUMBER: 137:230254
TITLE: Patterns of gene promoter methylation in squamous cell cancer of the head and neck
AUTHOR(S): Hasegawa, Masayuki; Nelson, Heather H.; Peters, Edward; Ringstrom, Elin; Posner, Marshall; Kelsey, Karl T.
CORPORATE SOURCE: Department of Cancer Cell Biology, Harvard School of Public Health, Boston, MA, 02115, USA
SOURCE: Oncogene (2002), 21(27), 4231-4236
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Promoter methylation is an important pathway in transcriptional silencing of known and candidate tumor suppressor genes in Head and Neck Squamous Cell Carcinoma (HNSCC). In order to study the association of tumor suppressor gene promoter methylation in HNSCC with patient clin. characteristics, especially alc. consumption and tobacco smoking, we examined promoter methylation of the p16INK4a, DAP-kinase, E-Cadherin, and RASSF1A genes using methylation-specific PCR (MSP) in 80 patients. The prevalence of p16INK4a, DAP-kinase, E-Cadherin, and RASSF1A promoter methylation was 26/80 (32.5%), 19/80 (23.8%), 29/80 (36.3%), 6/80 (7.5%) resp. In 48 cases (60%), at least one of these promoters was methylated. There was a significant association of methylation of any of these genes and ever smoking (P=0.006). P16INK4a gene promoter methylation was associated with a younger

age of smoking initiation (P<0.03). E-cadherin promoter methylation was associated with an increased number of pack years smoked (P<0.03). We also found an association of methylation of any gene and T status (OR=2.7, P<0.05). Tumors with p16INK4a methylation were significantly less likely to show lymph node metastasis (P<0.001). DAP-kinase promoter methylation was significantly associated with lymph node metastasis and this relationship was dependent upon p16INK4a promoter methylation status. Our results suggest that, in HNSCC, promoter methylation of these four genes accumulates with increasing tumor size. This may reflect distinct pathways of somatic inactivation leading to cancer; addnl. larger studies are needed to further investigate this possibility. Tobacco smoking may play an important role in both the occurrence of promoter methylation as well as delineating the precise pathway that eventually results in a tumorigenic phenotype.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:298786 HCAPLUS
DOCUMENT NUMBER: 137:45006
TITLE: Src kinase contributes to the metastatic spread of carcinoma cells
AUTHOR(S): Boyer, Brigitte; Bourgeois, Yveline; Poupon, Marie-France
CORPORATE SOURCE: UMR 146 CNRS, Institute Curie, Section de Recherche, Batiment 110 Centre Universitaire Paris-Sud, Orsay, 91405, Fr.
SOURCE: Oncogene (2002), 21(15), 2347-2356
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The involvement of Src kinase during carcinoma metastasis has been explored by using the NBT-II rat carcinoma cell line, which can be induced to scatter in vitro through Src activity. Here we show that Src activity was not required for growth of tumors derived from NBT-II cells injected into nude mice. In contrast, the presence of micrometastases was strictly dependent on Src, since the percentage of mice bearing metastases was dramatically reduced by the expression of a dominant-neg. mutant of Src (SrcK-) or of Csk, the natural inhibitor of Src. Furthermore, metastatic cells originating from NBT-II cells displayed a Src activity higher than the parental cells, confirming that Src gives a selective advantage during the metastatic process. Finally, anatomopathol. anal. of the primary tumors arising from NBT-II cells expressing Csk or SrcK- constructs revealed a highly differentiated epithelial phenotype contrasting with the poor differentiation of tumors derived from parental cells. The differentiated phenotype correlated with the presence of desmosomes at the cell periphery and the absence of vimentin intermediate filaments. Altogether, these data demonstrate that Src activity correlates with the loss of epithelial differentiation concomitantly with the increase of the metastatic potential of carcinoma cells.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:502052 HCAPLUS
DOCUMENT NUMBER: 132:91634
TITLE: Relationship between NDP **kinase** expression and **lymph node** metastasis in lung cancer of Yunnan tin miners
AUTHOR(S): Wang, Fang; Gao, Qian; Bai, Song; Sun, Laihua; Tian, Feng; Liu, Chonglin
CORPORATE SOURCE: Department of Pathology, Kunming Medical College, Kunming, 650031, Peop. Rep. China

SOURCE: Zhonghua Laodong Weisheng Zhiyebing Zazhi (1999), 17(3), 142-144
CODEN: ZLWZEX; ISSN: 1001-9391
PUBLISHER: Tianjinshi Laodong Weisheng Zhiyebing Yanjiuso
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Labeled streptavidin-biotin (LSAB) method was used to study the expression of nucleoside diphosphate kinase (NDPK), the product of metastasis suppressor gene nm23, and its correlation with lymph node metastasis in lung cancer of Yunnan tin miners. There was 57.9% (33/57) pos. expression of NDPK in lung cancer of Yunnan tin miners. The pos. staining rate was 56.4% (22/39) in squamous cell carcinoma and 61.1% (11/18) in adenocarcinoma without significant difference ($P > 0.05$). The NDPK expression in squamous cell carcinoma without hilar or mediastinal lymph node metastasis (18/29, 62.0%) was significantly increased as compared to that in squamous cell carcinoma with hilar or mediastinal lymph node metastasis (4/10, 40.0%). 12 (66.6%) Of 18 pos. staining in the former showed strong pos. staining whereas in the latter, no strong pos. staining was observed in 4 pos. staining ($P < 0.05$). There was no significant difference ($P > 0.05$) of NDPK expression between adenocarcinoma without hilar or mediastinal lymph node metastasis (10/13, 76.9%) and adenocarcinoma with hilar or mediastinal lymph node metastasis (1/5, 20.0%). Nm23 gene may play different roles in the pathogenesis and metastasis of pulmonary squamous cells carcinoma and adenocarcinoma of Yunnan tin miners. Its expression levels are inversely correlated with lymph node metastasis in pulmonary squamous cell carcinoma but not in adenocarcinoma.

L9 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:455521 HCAPLUS
DOCUMENT NUMBER: 125:218486
TITLE: Studies on the relationship between the expression of nm23 gene/NDP **kinase** and **lymph node** metastasis in oral squamous cell carcinoma
AUTHOR(S): Otsuki, Kaname
CORPORATE SOURCE: Dent. Sch., Okayama Univ., Okayama, 700, Japan
SOURCE: Okayama Shigakkai Zasshi (1996), 15(1), 73-86
CODEN: OSZAE3; ISSN: 0913-3941
PUBLISHER: Okayama Shigakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Nucleoside diphosphate kinase (NDPK)/nm23 was expressed as mRNA in basement membrane and a part of squamous cells in mucosa of rat tongue, and the patterns were similar between NDPKα and NDPKβ. Localization pattern of NDPKα protein was similar to the mRNA detection pattern, and NDPKβ protein localized more in squamous cell portion. NDPKβ expression was similar between normal mucosa and oral squamous cells, whereas NDPKα expression was in the tumor. The immunostaining of NDPKα might be applicable for the estimation of the metastasis of head neck cancer to cervical lymph nodes.

L9 ANSWER 8 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 1992:131331 BIOSIS
DOCUMENT NUMBER: PREV199242059031; BR42:59031
TITLE: SHEDDING OF THE C-NEU ONCOGENE PRODUCT INTO THE SERUM OF PATIENTS WITH BREAST CARCINOMA.
AUTHOR(S): KATH R K [Reprint author]; HOEFFKEN K; KUMMER G; LUEMMEN G; SCHEULEN M E; SEEBER S
CORPORATE SOURCE: INNERE KLIN UND POLIKLIN, TUMORFORSCHUNG, GERMANY
SOURCE: Onkologie, (1991) Vol. 14, No. SUPPL. 2, pp. 81-82.
Meeting Info.: ANNUAL GENERAL MEETING OF THE GERMAN AND AUSTRIAN SOCIETY FOR HEMATOLOGY AND ONCOLOGY, INNSBRUCK,

AUSTRIA, OCTOBER 10-13, 1991. ONKOLOGIE.
CODEN: ONKOD2. ISSN: 0378-584X.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 5 Mar 1992
Last Updated on STN: 6 Mar 1992

L9 ANSWER 9 OF 13 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 90094855 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2600272
TITLE: Flow cytometric analysis of protein **kinase** C in **lymph node** cells during the induction phase of contact hypersensitivity reaction.
AUTHOR: Morita H; Yamagata M; Inohara S; Sagami S
SOURCE: Journal of dermatology, (1989 Oct) 16 (5) 352-4.
Journal code: 7600545. ISSN: 0385-2407.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199002
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900206

AB On the fourth day after a single painting of 2,4,6-trinitro-chlorobenzene on the abdominal skin, inguinal lymph nodes were removed, and a single-cell suspension was prepared. The cells were analyzed flow cytometrically, using monoclonal anti-protein kinase C antibody. It was found that the number of lymph node cells in which protein kinase C was detected on the cell surface was significantly increased over that in non-treated mice (p less than 0.01). On the basis of our results and discussions in the literature, it is thought that protein kinase C is related to the initiation of the contact hypersensitivity reaction.

L9 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:54836 HCAPLUS
DOCUMENT NUMBER: 110:54836
TITLE: Fructose-2,6-bisphosphate in rat mesenteric lymph nodes
AUTHOR(S): Abuelgassim, A. O.; Khoja, S. M.
CORPORATE SOURCE: Fac. Sci., King Abdulaziz Univ., Jeddah, Saudi Arabia
SOURCE: International Journal of Biochemistry (1988), 20(10), 1185-8
CODEN: IJBOBV; ISSN: 0020-711X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The fructose 2,6-bisphosphate (Fru-2,6-P2) content of mesenteric lymph nodes was measured in rats. The effects of Fru-2,6-P2 on the activity of 6-phosphofructo-1-kinase (PFK-1) from rat mesenteric lymph nodes were also studied. The affinity of the enzyme for fructose 6-phosphate was increased by Fru-2,6-P2, whereas the inhibition of the enzyme with high concns. of ATP was released by Fru-2,6-P2. The activity of lymphocyte PFK-1 was highly stimulated in the simultaneous presence of low concns. of AMP and Fru-2,6-P2. These results show that rat lymphocyte PFK-1 is highly regulated by Fru-2,6-P2, which means that glycolysis in rat lymphocytes is controlled by Fru-2,6-P2.

L9 ANSWER 11 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 1988:369940 BIOSIS
DOCUMENT NUMBER: PREV198835054553; BR35:54553
TITLE: EPIDERMAL GROWTH FACTOR RECEPTOR GENE ABNORMALITIES IN HUMAN NON-SMALL CELL LUNG CANCER.

AUTHOR(S): SCHNEIDER P M [Reprint author]; HUNG M C; TAINSKY M A; GAZDAR A; AMES R S; ROTH J A
CORPORATE SOURCE: DEP THORACIC SURG, MD ANDERSON HOSP AND TUMOR INST, HOUSTON, TEXAS 77030, USA
SOURCE: Journal of Cellular Biochemistry Supplement, (1988) No. 12 PART A, pp. 113.
Meeting Info.: SYMPOSIUM ON GROWTH FACTORS AND THEIR RECEPTORS: GENETIC CONTROL AND RATIONAL APPLICATION HELD AT THE 17TH ANNUAL MEETING OF THE UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, JANUARY 24-30, 1988. J CELL BIOCHEM SUPPL.
ISSN: 0733-1959.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 9 Aug 1988
Last Updated on STN: 9 Aug 1988

L9 ANSWER 12 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 1986:240718 BIOSIS
DOCUMENT NUMBER: PREV198682005222; BA82:5222
TITLE: FOLLOW-UP OF SETTLEMENT AND MITOSIS OF LEUKEMIC LYMPHOBLASTS BY ENZYME ACTIVITY DETERMINATION IN AKR AND HSS INBRED MICE THE EFFECT OF GENETIC FACTORS.
AUTHOR(S): ARANY I [Reprint author]; KERTAI P
CORPORATE SOURCE: DEBRECENI ORVOSTUDOMANYI EGYETEM KOZEGESZSEGTANI ES JARVANYTANI INTEZETE, DEBRECEN
SOURCE: Magyar Onkologia, (1986) Vol. 30, No. 1, pp. 32-37.
CODEN: MGONAD. ISSN: 0025-0244.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: HUNGARIAN
ENTRY DATE: Entered STN: 7 Jun 1986
Last Updated on STN: 7 Jun 1986
AB The authors transplanted lymphoid leukaemic cells of AKR and HSS origin into AKR and HSS + AKR/F1 mice and studied the changes of pyruvate kinase activity in the thymus, lymph nodes, spleen and plasma on the days after transplantation. Data were obtained on the settlement and mitosis of leukaemic lymphoblasts. The results suggest that this model is suitable to study the fate of the transplanted tumor cells and the genetic factors influencing the transplantation.

L9 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1962:419065 HCAPLUS
DOCUMENT NUMBER: 57:19065
ORIGINAL REFERENCE NO.: 57:3904g-i
TITLE: Thymidine phosphorylation and deoxyribonucleic acid (DNA) synthesis in human leukemic cells
AUTHOR(S): Bianchi, P. A.
CORPORATE SOURCE: Chester Beatty Res. Inst., London
SOURCE: Biochimica et Biophysica Acta (1962), 55, 547-9
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB cf. CA 56, 9088b. Samples of supernatant fractions from normal and leukemic human leukocytes, lymph nodes, and spleen were examined for thymidine kinases and DNA polymerase activity. The content of DNA polymerase appeared to reflect the proliferative capacity of the cell or tissue system, while there was evidence that the content of thymidylate kinase reflected the rate of cell division. The thymidine kinase activity was very low; the importance of this finding is discussed relative to the use of thymidine as a precursor in studies of DNA synthesis.

```
=> d his

     (FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1       1280537 S KINASE?
L2        385991 S LYMPH(A)NODE?
L3         65436 S STROMAL(W)CELL
L4          5129 S L1 AND L2
L5            92 S L3 AND L4
L6            50 DUP REM L5 (42 DUPLICATES REMOVED)
L7             0 S L3(W)L2(W)L1
L8            15 S L1(2W)L2
L9            13 DUP REM L8 (2 DUPLICATES REMOVED)

=> s clon? or express? or recombinant
   4 FILES SEARCHED...
L10     6902623 CLON? OR EXPRESS? OR RECOMBINANT

=> s (l6 or l9) and l10
L11           50 (L6 OR L9) AND L10

=> s murine or mouse
L12     3908319 MURINE OR MOUSE

=> s MLKS##
L13          176 MLKS##

=> s l12 and l143
L143 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l12 and l13
L14           31 L12 AND L13

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15           11 DUP REM L14 (20 DUPLICATES REMOVED)

=> d 1-11 ibib ab

L15  ANSWER 1 OF 11     MEDLINE on STN
ACCESSION NUMBER:    2004349762     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 15069087
TITLE:               Mixed lineage kinase 3 (MLK3)-activated p38 MAP kinase
                     mediates transforming growth factor-beta-induced apoptosis
                     in hepatoma cells.
AUTHOR:              Kim Ki-Yong; Kim Byung-Chul; Xu Zhiheng; Kim Seong-Jin
CORPORATE SOURCE:    Laboratory of Cell Regulation and Carcinogenesis, NCI,
                     National Institutes of Health, Bethesda, Maryland 20892,
                     USA.
SOURCE:              Journal of biological chemistry, (2004 Jul 9) 279 (28)
                     29478-84.
                     Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200408
ENTRY DATE:          Entered STN: 20040716
```

Last Updated on STN: 20040825
Entered Medline: 20040824

AB Although transforming growth factor beta1 (TGF-beta1) acts via the Smad signaling pathway to initiate de novo gene transcription, the TGF-beta1-induced MAPK kinase activation that is involved in the regulation of apoptosis is less well understood. Even though the p38 MAP kinase and c-Jun NH(2)-terminal kinases (JNKs) are involved in TGF-beta1-induced cell death in hepatoma cells, the upstream mediators of these kinases remain to be defined. We show here that the members of the mixed lineage kinase (MLK) family (including MLK1, MLK2, MLK3, and dual leucine zipper-bearing kinase (DLK)) are expressed in FaO rat hepatoma cells and are likely to act between p38 and TGF-beta receptor kinase in death signaling. TGF-beta1 treatment leads to an increase in MLK3 activity. Overexpression of MLK3 enhances TGF-beta1-induced apoptotic death in FaO cells and Hep3B human hepatoma cells, whereas expression of the dominant-negative forms of MLK3 suppresses cell death induced by TGF-beta1. The dominant-negative forms of MLK1 and -2 also suppress TGF-beta1-induced cell death. In MLK3-overexpressing cells, ERK, JNKs, and p38 MAP kinases were further activated in response to TGF-beta1 compared with the control cells. In contrast, overexpression of the dominant-negative MLK3 resulted in suppression of TGF-beta1-induced MAP kinase activation and TGF-beta1-induced caspase-3 activation. We also show that only the inhibition of the p38 pathway suppressed TGF-beta1-induced apoptosis. These observations support a role for **MLKs** in the TGF-beta1-induced cell death mechanism.

L15 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004391161 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15294995
TITLE: Specific modulation of astrocyte inflammation by inhibition of mixed lineage kinases with CEP-1347.
AUTHOR: Falsig Jeppe; Porzgen Peter; Lotharius Julie; Leist Marcel
CORPORATE SOURCE: H. Lundbeck, Valby, Denmark.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Aug 15) 173 (4) 2762-70.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040806
Last Updated on STN: 20040929
Entered Medline: 20040928

AB Inflammatory conversion of **murine** astrocytes correlates with the activation of various MAPK, and inhibition of terminal MAPKs like JNK or p38 dampens the inflammatory reaction. Mixed lineage kinases (**MLKs**), a family of MAPK kinase kinases, may therefore be involved in astrocyte inflammation. In this study, we explored the effect of the MLK inhibitors CEP-1347 and CEP-11004 on the activation of **murine** astrocytes by either TNF plus IL-1 or by a complete cytokine mix containing additional IFN-gamma. The compounds blocked NO-, PG-, and IL-6 release with a median inhibitory concentration of approximately 100 nM. This activity correlated with a block of the JNK and the p38 pathways activated in complete cytokine mix-treated astrocytes. Although CEP-1347 did not affect the activation of NF-kappaB, it blocked the expression of cyclooxygenase-2 and inducible NO synthase at the transcriptional level. Quantitative transcript profiling of 17 inflammation-linked genes revealed a specific modulation pattern of astrocyte activation by MLK inhibition, for instance, characterized by up-regulation of the anti-stress factors inhibitor of apoptosis protein-2 and activated transcription factor 4, no effect on manganese superoxide dismutase and caspase-11, and down-regulation of major inflammatory players like TNF, GM-CSF, urokinase-type plasminogen activator, and IL-6. In conclusion, MLK

inhibitors like CEP-1347 are highly potent astrocyte immune modulators with a novel spectrum of activity.

L15 ANSWER 3 OF 11 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004001981 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14697235
TITLE: SP3 acts as a positive regulator on the core promoter of human ZPK gene.
AUTHOR: Itoh Aki; Wang Zhili; Ito Yasuhiro; Reddy Usha R; Itoh Takayuki
CORPORATE SOURCE: Division of Neurology Research, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.
CONTRACT NUMBER: NS08075 (NINDS)
NS25044 (NINDS)
SOURCE: Biochemical and biophysical research communications, (2004 Jan 16) 313 (3) 612-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF283474; GENBANK-AF283475
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20040106
Last Updated on STN: 20040218
Entered Medline: 20040217

AB ZPK (zipper protein kinase)/MUK/DLK/MAP3K12, a member of mixed-lineage kinases (**MLKs**), is expressed in a tissue-specific manner, particularly in developing brain, and likely to contribute to cytodifferentiation, apoptotic elimination, and migration. To understand the preferential expression of ZPK in neuronal tissues, we have analyzed the putative core promoter region upstream of the first exon of the human ZPK gene. The core promoter region is TATA-less, but contains several potential transcription factor-binding motifs such as a GC-box, all of which are well conserved between human and **mouse**. Reporter assays and 'gel-shift' analysis using SH-SY5Y cells revealed that a xenobiotic responsive element (XRE)-like motif (GGGCGTGTCC) was preferentially recognized by Sp3, and enhanced the core promoter activity. However, the core promoter activity was still potent even in HeLa cells which barely express ZPK. Our results suggest that, for the selective expression of ZPK gene, cell-specific negative regulatory element(s) which locate outside of the core promoter region repress the potent basic promoter activity.

L15 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004127693 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15019567
TITLE: Inhibition of mixed lineage kinase 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells.
AUTHOR: Mathiasen Joanne R; McKenna Beth Ann W; Saporito Michael S; Ghadge Ghanashyam D; Roos Raymond P; Holskin Beverly P; Wu Zhi-Liang; Trusko Stephen P; Connors Thomas C; Maroney Anna C; Thomas Beth Ann; Thomas Jeffrey C; Bozyczko-Coyne Donna
CORPORATE SOURCE: Neurobiology, Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380, USA.
SOURCE: Brain research, (2004 Apr 2) 1003 (1-2) 86-97.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 20040316
Last Updated on STN: 20040721

Entered Medline: 20040720

AB The neuropathology of Parkinson's Disease has been modeled in experimental animals following MPTP treatment and in dopaminergic cells in culture treated with the MPTP neurotoxic metabolite, MPP(+). MPTP through MPP(+) activates the stress-activated c-Jun N-terminal kinase (JNK) pathway in **mice** and SH-SY5Y neuroblastoma cells. Recently, it was demonstrated that CEP-1347/KT7515 attenuated MPTP-induced nigrostriatal dopaminergic neuron degeneration in **mice**, as well as MPTP-induced JNK phosphorylation. Presumably, CEP-1347 acts through inhibition of at least one upstream kinase within the mixed lineage kinase (MLK) family since it has been shown to inhibit MLK 1, 2 and 3 in vitro. Activation of the MLK family leads to JNK activation. In this study, the potential role of MLK and the JNK pathway was examined in MPP(+)-induced cell death of differentiated SH-SY5Y cells using CEP-1347 as a pharmacological probe and dominant negative adenoviral constructs to **MLKs**. CEP-1347 inhibited MPP(+)-induced cell death and the morphological features of apoptosis. CEP-1347 also prevented MPP(+)-induced JNK activation in SH-SY5Y cells. Endogenous MLK 3 expression was demonstrated in SH-SY5Y cells through protein levels and RT-PCR. Adenoviral infection of SH-SY5Y cells with a dominant negative MLK 3 construct attenuated the MPP(+)-mediated increase in activated JNK levels and inhibited neuronal death following MPP(+) addition compared to cultures infected with a control construct. Adenoviral dominant negative constructs of two other MLK family members (MLK 2 and DLK) did not protect against MPP(+)-induced cell death. These studies show that inhibition of the MLK 3/JNK pathway attenuates MPP(+)-mediated SH-SY5Y cell death in culture and supports the mechanism of action of CEP-1347 as an MLK family inhibitor.

L15 ANSWER 5 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2003292421 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12818176
TITLE: JNK-mediated BIM phosphorylation potentiates BAX-dependent apoptosis.
AUTHOR: Putcha Girish V; Le Siyuan; Frank Stephan; Besirli Cagri G; Clark Kim; Chu Boyang; Alix Shari; Youle Richard J; LaMarche Art; Maroney Anna C; Johnson Eugene M Jr
CORPORATE SOURCE: Department of Neurology and Department of Molecular Biology and Pharmacology, Washington University School of Medicine, Saint Louis, MO 63110, USA.
CONTRACT NUMBER: R01NS38651 (NINDS)
R37AG-12947 (NIA)
SOURCE: Neuron, (2003 Jun 19) 38 (6) 899-914.
Journal code: 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030624
Last Updated on STN: 20030816
Entered Medline: 20030815

AB Trophic factor deprivation (TFD) activates c-Jun N-terminal kinases (JNKs), culminating in coordinate AP1-dependent transactivation of the BH3-only BCL-2 proteins BIM(EL) and HRK, which in turn are critical for BAX-dependent cytochrome c release, caspase activation, and apoptosis. Here, we report that TFD caused not only induction but also phosphorylation of BIM(EL). Mitochondrially localized JNKs but not upstream activators, like mixed-lineage kinases (**MLKs**) or mitogen-activated protein kinase kinases (MKKs), specifically phosphorylated BIM(EL) at Ser65, potentiating its proapoptotic activity. Inhibition of the JNK pathway attenuated BIM(EL) expression, prevented BIM(EL) phosphorylation, and abrogated TFD-induced apoptosis. Conversely, activation of this pathway promoted BIM(EL) expression and

phosphorylation, causing BIM- and BAX-dependent cell death. Thus, JNKs regulate the proapoptotic activity of BIM(EL) during TFD, both transcriptionally and posttranslationally.

L15 ANSWER 6 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2003007754 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12514131
TITLE: POSH acts as a scaffold for a multiprotein complex that mediates JNK activation in apoptosis.
AUTHOR: Xu Zhiheng; Kukekov Nickolay V; Greene Lloyd A
CORPORATE SOURCE: Department of Pathology and Center for Neurobiology and Behavior, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
CONTRACT NUMBER: T32-DK07328-22 (NIDDK)
SOURCE: EMBO journal, (2003 Jan 15) 22 (2) 252-61.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030107
Last Updated on STN: 20030226
Entered Medline: 20030225

AB We report that the multidomain protein POSH (plenty of SH3s) acts as a scaffold for the JNK pathway of neuronal death. This pathway consists of a sequential cascade involving activated Rac1/Cdc42, mixed-lineage kinases (**MLKs**), MAP kinase kinases (MKKs) 4 and 7, c-Jun N-terminal kinases (JNKs) and c-Jun, and is required for neuronal death induced by various means including nerve growth factor (NGF) deprivation. In addition to binding GTP-Rac1 as described previously, we find that POSH binds **MLKs** both in vivo and in vitro, and complexes with MKKs 4 and 7 and with JNKs. POSH overexpression promotes apoptotic neuronal death and this is suppressed by dominant-negative forms of **MLKs**, MKK4/7 and c-Jun, and by an MLK inhibitor. Moreover, a POSH antisense oligonucleotide and a POSH small interfering RNA (siRNA) suppress c-Jun phosphorylation and neuronal apoptosis induced by NGF withdrawal. Thus, POSH appears to function as a scaffold in a multiprotein complex that links activated Rac1 and downstream elements of the JNK apoptotic cascade.

L15 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:1465 HCAPLUS
DOCUMENT NUMBER: 136:363246
TITLE: Mixed lineage kinase activity of indolocarbazole analogues
AUTHOR(S): Murakata, Chikara; Kaneko, Masami; Gessner, George; Angeles, Thelma S.; Ator, Mark A.; O'Kane, Teresa M.; McKenna, Beth Ann W.; Thomas, Beth Ann; Mathiasen, Joanne R.; Saporito, Michael S.; Bozyczko-Coyne, Donna; Hudkins, Robert L.
CORPORATE SOURCE: Kyowa-Hakko Kogyo Co., Ltd., Tokyo, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(2), 147-150
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The MLK1-3 activity for a series of analogs of the indolocarbazole K-252a is reported. Addition of 3,9-bis-alkylthiomethyl groups to K-252a results in potent and selective MLK inhibitors. The in vitro and in vivo neuronal survival promoting activity of bis-isopropylthiomethyl-K-252a (CEP-11004/KT-8138) is reported. CEP-11004 demonstrated protection of the JNK kinase pathway following treatment of cells with MPP+ and demonstrated in vivo protection of dopaminergic terminals with the striatum projecting

from neurons within the substantia nigra om **mice** following administration of MPTP. Thus, inhibition of **MLKs** may be an effective strategy for blocking neurodegeration association with Parkinson's disease.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 11 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001376734 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11325962
TITLE: Cep-1347 (KT7515), a semisynthetic inhibitor of the mixed lineage kinase family.
AUTHOR: Maroney A C; Finn J P; Connors T J; Durkin J T; Angeles T; Gessner G; Xu Z; Meyer S L; Savage M J; Greene L A; Scott R W; Vaught J L
CORPORATE SOURCE: Cephalon Inc., 145 Brandywine Pkwy., West Chester, Pennsylvania 19380, USA.. amaroney@cephalon.com
SOURCE: Journal of biological chemistry, (2001 Jul 6) 276 (27) 25302-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20030105
Entered Medline: 20010809

AB CEP-1347 (KT7515) promotes neuronal survival at dosages that inhibit activation of the c-Jun amino-terminal kinases (JNKs) in primary embryonic cultures and differentiated PC12 cells after trophic withdrawal and in **mice** treated with 1-methyl-4-phenyl tetrahydropyridine. In an effort to identify molecular target(s) of CEP-1347 in the JNK cascade, JNK1 and known upstream regulators of JNK1 were co-expressed in Cos-7 cells to determine whether CEP-1347 could modulate JNK1 activation. CEP-1347 blocked JNK1 activation induced by members of the mixed lineage kinase (MLK) family (MLK3, MLK2, MLK1, dual leucine zipper kinase, and leucine zipper kinase). The response was selective because CEP-1347 did not inhibit JNK1 activation in cells induced by kinases independent of the MLK cascade. CEP-1347 inhibition of recombinant MLK members in vitro was competitive with ATP, resulting in IC(50) values ranging from 23 to 51 nm, comparable to inhibitory potencies observed in intact cells. In addition, overexpression of MLK3 led to death in Chinese hamster ovary cells, and CEP-1347 blocked this death at doses comparable to those that inhibited MLK3 kinase activity. These results identify **MLKs** as targets of CEP-1347 in the JNK signaling cascade and demonstrate that CEP-1347 can block MLK-induced cell death.

L15 ANSWER 9 OF 11 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:497464 BIOSIS
DOCUMENT NUMBER: PREV200100497464
TITLE: CEP-11004 as a pharmacological tool for assessing the role of the mixed lineage kinase pathway in MPTP-mediated cell death processes.
AUTHOR(S): McKenna, B. A. W. [Reprint author]; Thomas, B. A. [Reprint author]; Gessner, G. W. [Reprint author]; Husten, E. J. [Reprint author]; Hudkins, R. L. [Reprint author]; Bozyczko-Coyne, D. [Reprint author]; Mathiasen, J. R. [Reprint author]; Saporito, M. S. [Reprint author]
CORPORATE SOURCE: Neurobiology, Cephalon Inc, West Chester, PA, USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 524. print.
Meeting Info.: 31st Annual Meeting of the Society for

Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Oct 2001
Last Updated on STN: 23 Feb 2002

AB Activation of the c-jun N-terminal kinase (JNK) pathway is a critical mediator in some forms of apoptotic neuronal death and may be an important component in MPTP (MPP+)-mediated nigrostriatal dopaminergic neuronal death. One pathway for regulation of JNK signaling is via activation of MKK4 through upstream stimulation of the mixed lineage kinase (MLK) family. CEP-11004 has been identified as an inhibitor of the MLK family of kinases and may be a useful pharmacological tool for investigating the role of **MLKs** in cellular processes. The present studies were designed to investigate the role of **MLKs**, using CEP-11004, in regulating MPP+-mediated neuronal death in culture and in vivo. MPP+ elevated levels of phosphorylated JNK (p-JNK) and produced cell death as measured by release of LDH in neuronally differentiated SH-SY5Y neuroblastoma cells. Inclusion of CEP-11004 in the culture media (100nM) attenuated the MPP+-mediated increase in p-JNK levels and blocked MPP+-mediated neuronal death. In **mice**, subcutaneous administration of CEP-11004 attenuated the MPTP-mediated elevations in p-MKK4 and p-JNK in the substantia nigra and, with longer survival times, attenuated MPTP-mediated nigrostriatal dopaminergic neuronal death. These studies and those with another MLK family inhibitor, CEP-1347, support activation of the MLK pathway as a potential route for MPP+-mediated dopaminergic death in culture and in vivo and indicate that CEP-11004 can be employed as a pharmacological tool for investigating the role of **MLKs** in neuronal death processes.

L15 ANSWER 10 OF 11 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:486426 BIOSIS
DOCUMENT NUMBER: PREV200100486426
TITLE: CEP-1347 (KT7515) is an inhibitor of the mixed lineage kinase family.
AUTHOR(S): Maroney, A. C. [Reprint author]; Finn, J. P. [Reprint author]; Connors, T. J. [Reprint author]; Durkin, J. T. [Reprint author]; Angeles, T. [Reprint author]; Gessner, G. [Reprint author]; Xu, Z.; Meyer, S. L. [Reprint author]; Savage, M. J. [Reprint author]; Greene, L. G.; Scott, R. W. [Reprint author]; Vaught, J. L. [Reprint author]
CORPORATE SOURCE: Neurobiology, Cephalon Inc, West Chester, PA, USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 28. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 2001
Last Updated on STN: 23 Feb 2002

AB The semi-synthetic compound, CEP-1347 (KT7515), has been demonstrated to protect multiple neuronal cell types from a variety of insults leading to programmed cell death. CEP-1347 prevents neuronal loss at dosages that lead to inhibition of c-Jun Amino-Terminal Kinase (JNK) activation in primary embryonic cultures and differentiated PC12 cells after trophic withdrawal and in **mice** treated with 1-methyl-4-phenyl tetrahydropyridine. To further explore the molecular target of CEP-1347 in the JNK cascade, JNK1 and known upstream regulators of JNK1 were

co-expressed in Cos-7 cells to determine if CEP-1347 could modulate JNK1 activation. CEP-1347 blocked JNK1 activation induced by members of the Mixed Lineage Kinase family (MLK3, MLK2, MLK1, DLK, LZK). The response was selective since CEP-1347 did not inhibit JNK1 activation in cells induced by kinases independent of the MLK cascade. Inhibition of recombinant MLK members in vitro by CEP-1347 was competitive with ATP resulting in IC50 values ranging from 23-51 nM, comparable to inhibitory potencies observed in intact cells. In addition, overexpression of MLK3 led to death in CHO cells, and CEP-1347 blocked this death at doses comparable to those that inhibited MLK3 kinase activity. These results identify **MLKs** as targets of CEP-1347 in the JNK signaling cascade, and demonstrate that CEP-1347 can block MLK-induced cell death.

L15 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999247568 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10232608
TITLE: The JNK/SAPK activator mixed lineage kinase 3 (MLK3) transforms NIH 3T3 cells in a MEK-dependent fashion.
AUTHOR: Hartkamp J; Troppmair J; Rapp U R
CORPORATE SOURCE: Institut fur Medizinische Strahlenkunde und Zellforschung, Universitat Wurzburg, Germany.
SOURCE: Cancer research, (1999 May 1) 59 (9) 2195-202. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20000303
Entered Medline: 19990520

AB Mixed lineage kinases (**MLKs**) form a family of serin/threonine protein kinases with multiple protein/protein interaction domains (SH3, Cdc42 Rac interactive binding sequence, leucine zipper, and proline rich region), the physiological roles of which are largely unknown. We show that overexpression of wild type MLK3 leads to morphological transformation of NIH 3T3 fibroblasts and growth in soft agar. Consistent with this transforming potential, we demonstrate that MLK3 strongly induces transcription from a reporter construct that is driven by a composite AP-1-/Ets-1-enhancer element in HEK 293 cells. In the same cell system, MLK3 preferentially activates the c-Jun NH2-terminal kinase/stress-activated protein kinase (JNK/SAPK) mitogen-activated protein kinase cascade and to a lesser degree the extracellular signal-regulated kinase (ERK) pathway. Activation of the latter can be further enhanced by coexpression of wild type MEK1 and is blocked by the synthetic MEK inhibitor PD 098059 or a kinase-dead MEK1 mutant. Immunoprecipitated MLK3 catalyses the phosphorylation of MEK1 in vitro, but this phosphorylation leads only to a marginal activation. In support of these data, we also show that MEK1 is highly phosphorylated in vivo on Ser 217/221 in MLK3-transformed fibroblasts, whereas activating ERK phosphorylations are barely detectable. Nevertheless, MLK3-transformed NIH 3T3 fibroblasts are partially reverted when activation of MEK is specifically blocked with PD 098059. Our combined data show that although MLK3 is primarily an activator of the JNK/SAPK pathway, overexpression of the wild type protein leads to a transformed phenotype in NIH 3T3 cells that can be partially reversed by a synthetic MEK inhibitor. We conclude that the ERK pathway is necessary for MLK3-mediated transformation.

=> d his

(FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,

```
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1      1280537 S KINASE?
L2       385991 S LYMPH(A)NODE?
L3        65436 S STROMAL(W)CELL
L4         5129 S L1 AND L2
L5           92 S L3 AND L4
L6           50 DUP REM L5 (42 DUPLICATES REMOVED)
L7            0 S L3(W)L2(W)L1
L8           15 S L1(2W)L2
L9           13 DUP REM L8 (2 DUPLICATES REMOVED)
L10     6902623 S CLON? OR EXPRESS? OR RECOMBINANT
L11          50 S (L6 OR L9) AND L10
L12     3908319 S MURINE OR MOUSE
L13         176 S MLKS##
L14          31 S L12 AND L13
L15          11 DUP REM L14 (20 DUPLICATES REMOVED)

=> s l6 and l12
L16          24 L6 AND L12

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17          24 DUP REM L16 (0 DUPLICATES REMOVED)

=> d 1-24 ibib ab

L17  ANSWER 1 OF 24  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:371064  HCAPLUS
DOCUMENT NUMBER:          140:373461
TITLE:                    Evaluation of breast cancer states and outcomes using
                          gene expression profiles
INVENTOR(S):              West, Mike; Nevins, Joseph R.; Huang, Andrew
PATENT ASSIGNEE(S):       Synpac, Inc., USA; Duke Univerisity
SOURCE:                   PCT Int. Appl., 799 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   5
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2004037996         A2    20040506    WO 2003-US33656         20031024
     WO 2004037996         A3    20041229
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2004083084         A1    20040429    US 2002-291878          20021112
     WO 2004044839         A2    20040527    WO 2002-US38216         20021112
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT,
             TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
```

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004106113	A1	20040603	US 2002-291886		20021112
PRIORITY APPLN. INFO.:			US 2002-420729P	P	20021024
			US 2002-421062P	P	20021025
			US 2002-421102P	P	20021025
			US 2002-424701P	P	20021108
			US 2002-424715P	P	20021108
			US 2002-424718P	P	20021108
			US 2002-291878	A	20021112
			US 2002-291886	A	20021112
			US 2002-425256P	P	20021112
			WO 2002-US38216	A	20021112
			WO 2002-US38222	A	20021112
			US 2003-448461P	P	20030221
			US 2003-448462P	P	20030221
			US 2003-457877P	P	20030327
			US 2003-458373P	P	20030331

AB The present invention relates generally to a method for evaluating and/or predicting breast cancer states and outcomes by measuring gene and metagene expression levels and integrating such data with clin. risk factors. Genes and metagenes whose expressions are correlated with a particular breast cancer risk factor or phenotype are provided using binary prediction tree modeling. The invention provides 175 genes associated with metagene predictors of **lymph node** metastasis, 216 genes associated with metagene predictors of breast cancer recurrence, and 496 metagenes related to breast cancer study. Methods of using the subject genes and metagenes in diagnosis and treatment methods, as well as drug screening methods, etc are also provided. In addition, reagents, media and kits that find use in practicing the subject methods are also provided.

L17 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:308529 HCAPLUS
DOCUMENT NUMBER: 140:333599
TITLE: Gene expression profile of human and **mouse** genes in atopic dermatitis and psoriasis patients and its use for diagnosis, therapy, and drug screening
INVENTOR(S): Itoh, Mikito; Ogawa, Kaoru; Shinagawa, Akira; Sudo, Hajime; Ogawa, Hideoki; Ra, Chisei; Mitsuishi, Kouichi
PATENT ASSIGNEE(S): Genox Research, Inc., Japan; Juntendo University
SOURCE: PCT Int. Appl., 611 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004031386	A1	20040415	WO 2003-JP9808	20030801

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:	JP 2002-229318	A	20020806
	JP 2003-136543	A	20030514

AB This invention provides gene expression profile between a rash site and a

no-rash site in a patient with atopic dermatitis or a patient with psoriasis. The invention also provides gene expression profile between a no-rash site in such a disease and a normal subject. Animal models, particularly **mouse** for those diseases are also claimed. The gene expression profile provided in this invention can be used for diagnosis, therapy, and drug screening for atopic dermatitis and psoriasis.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2004627248 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15585839
TITLE: Intestinal cryptopatch formation in **mice** requires lymphotoxin alpha and the lymphotoxin beta receptor.
AUTHOR: Taylor Rebekah T; Lugering Andreas; Newell Kenneth A; Williams Ifor R
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA.
CONTRACT NUMBER: DK64399 (NIDDK)
DK64730 (NIDDK)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Dec 15) 173 (12) 7183-9.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20041220
Last Updated on STN: 20041220

AB Interactions between lymphotoxin (LT)alpha(1)beta(2) on inducer cells and the lymphotoxin beta receptor (LTbetaR) on **stromal cells** initiate development of **lymph nodes** and Peyer's patches. In this study, we assessed the contributions of LTalpha and LTbetaR to the development of cryptopatches (CP), aggregates of T cell precursors in the **mouse** small intestine. **Mice** genetically deficient in LTalpha or LTbetaR lacked CP. Bone marrow from LTalpha-deficient **mice** was unable to initiate development of CP or isolated lymphoid follicles (ILF) after transfer to CD132-null **mice** lacking CP and ILF. However, LTalpha-deficient bone marrow-derived cells contributed to CP formed in CD132-null **mice** receiving a mixture of wild-type and LTalpha-deficient bone marrow cells. Transfer of wild-type bone marrow into irradiated LTalpha-deficient **mice** resulted in reconstitution of both CP and ILF. However, the LT-dependent formation of CP was distinguished from the LT-dependent formation of ILF and Peyer's patches by not requiring the presence of an intact NF-kappaB-inducing **kinase** gene. CP but not ILF were present in the small intestine from NF-kappaB-inducing **kinase** -deficient alymphoplasia **mice**, indicating that the alternate NF-kappaB activation pathway required for other types of LTbetaR-dependent lymphoid organogenesis is dispensable for CP development. In addition, we identified VCAM-1(+) cells within both CP and ILF that are candidates for the **stromal cells** involved in receiving LT-dependent signals from the hemopoietic precursors recruited to CP. These findings demonstrate that interactions between cells expressing LTalpha(1)beta(2) and LTbetaR are a shared feature in the development of all small intestinal lymphoid aggregates.

L17 ANSWER 4 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2004572999 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15492752
TITLE: Acquisition of **lymph node**, but not distant metastatic potentials, by the overexpression of

CXCR4 in human oral squamous cell carcinoma.
AUTHOR: Uchida Daisuke; Begum Nasima-Mila; Tomizuka Yoshifumi; Bando Takashi; Almofti Ammar; Yoshida Hideo; Sato Mitsunobu
CORPORATE SOURCE: Second Department of Oral and Maxillofacial Surgery, Tokushima University School of Dentistry, Kuramoto, Tokushima, Japan.. daisuke@dent.tokushima-u.ac.jp
SOURCE: Laboratory investigation; a journal of technical methods and pathology, (2004 Dec) 84 (12) 1538-46.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041117
Last Updated on STN: 20041220

AB Recently, it has been suggested that chemokine/receptor interactions determine the destination of the invasive tumor cells in several types of cancer. It has also been proposed that the **stromal cell** -derived factor-1 (SDF-1; CXCL12)/CXCR4 system might be involved **lymph node** metastasis in oral squamous cell carcinoma (SCC). In order to further clarify the role of the SDF-1/CXCR4 system in oral SCC, we generated CXCR4 stable transfectants (IH-CXCR4) using oral SCC cells, and compared them to IH, which did not express CXCR4 and which did not have **lymph node** metastatic potentials in vivo. We introduced enhanced green fluorescent protein (GFP) fused-CXCR4 into IH cells, and detected the GFP fluorescence in the cytoplasm and cell membrane in approximately 60% of the G418-resistant cells. This bulk-transfectant expressed a high level of CXCR4 mRNA and protein, and exhibited the characteristic calcium fluxes and chemotactic activity observed in treatment with SDF-1. SDF-1 biphasically activated extracellular signal-regulated **kinase** (ERK)1/2, but continuously activated Akt/protein **kinase** B (PKB) in IH-CXCR4 cells. Most importantly, IH-CXCR4 cells frequently metastasized to the cervical **lymph node**, but not to the distant organs in the orthotopic inoculation of nude **mice**. Furthermore, these **lymph node** metastases were inhibited by the treatment of a mitogen-activated protein **kinase**/ERK **kinase** inhibitor, U0126, or a phosphatidylinositol 3 **kinase** inhibitor, wortmannin. These results indicate that SDF-1/CXCR4 signaling mediates the establishment of **lymph node** metastasis in oral SCC via ERK1/2 or Akt/PKB pathway.

L17 ANSWER 5 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2004286637 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15186750
TITLE: Requirement for Tec **kinases** in chemokine-induced migration and activation of Cdc42 and Rac.
AUTHOR: Takesono Aya; Horai Reiko; Mandai Michiko; Dombroski Derek; Schwartzberg Pamela L
CORPORATE SOURCE: National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: Current biology : CB, (2004 May 25) 14 (10) 917-22.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 20040610
Last Updated on STN: 20040721
Entered Medline: 20040720

AB Cell polarization and migration in response to chemokines is essential for proper development of the immune system and activation of immune responses. Recent studies of chemokine signaling have revealed a critical

role for PI3-**Kinase**, which is required for polarized membrane association of pleckstrin homology (PH) domain-containing proteins and activation of Rho family GTPases that are essential for cell polarization and actin reorganization. Additional data argue that tyrosine **kinases** are also important for chemokine-induced Rac activation. However, how and which **kinases** participate in these pathways remain unclear. We demonstrate here that the Tec **kinases** Itk and Rlk play an important role in chemokine signaling in T lymphocytes. Chemokine stimulation induced transient membrane association of Itk and phosphorylation of both Itk and Rlk, and purified T cells from Rlk(-/-)Itk(-/-) **mice** exhibited defective migration to multiple chemokines in vitro and decreased homing to **lymph nodes** upon transfer to wt **mice**. Expression of a dominant-negative Itk impaired SDF-1alpha-induced migration, cell polarization, and activation of Rac and Cdc42. Thus, Tec **kinases** are critical components of signaling pathways required for actin polarization downstream from both antigen and chemokine receptors in T cells.

L17 ANSWER 6 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:288935 BIOSIS
DOCUMENT NUMBER: PREV200400287692
TITLE: Differential TNFR and LT beta R regulation of High Endothelial Venule (HEV) Specific Genes.
AUTHOR(S): Liao, Shan [Reprint Author]; Lesslauer, Werner; Ruddle, Nancy H
CORPORATE SOURCE: Epidemiology and Public Health, Yale University School of Medicine, 60 College Street, New Haven, CT, 06520-8034, USA shan.liao@yale.edu
SOURCE: FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 332.1. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004

AB HEVs are specialized **lymph node** blood vessels where lymphocyte trafficking occurs. Optimal HEV function may be regulated at the level of gene expression of glycoproteins (GlyCAM-1, MAdCAM-1), chemokines (SLC) and posttranslational modifying enzymes (FucTIV, FucTVII, and an HEV specific GlcNAc-6-sulfotransferase (HEC-6ST)). We have previously determined that LTbR signaling contributes to HEV and HEC6ST in LTb-/- and in RIPLTab transgenic **mice**. Both the classical and alternative NF-kB pathways have been implicated in LTbR signal transduction in fibroblasts and spleen cells. However, it was not clear whether LTab could directly stimulate endothelial cells and/or whether its effect was mediated through **stromal cells**, which in turn activate HEV gene expression. Endothelial cell lines, bEND.3 and SVEC, were adopted as an in vitro system to evaluate and compare LTbR and TNFR mediated signaling for endothelial and HEV specific genes. FACS analysis revealed LTbR surface expression on both cell lines. Several genes were differentially induced by treatment with LTbR agonistic antibody or TNF. The signaling pathways regulating gene expression also differed as revealed by treatment with **kinase** or NF-kB inhibitors. Therefore, LTab has the capacity to directly activate endothelial cells and the pathways and genes differ from those employed by TNF. Supported by NIH CA16885 and the Anna Fuller Fund for Cancer Research.

L17 ANSWER 7 OF 24 MEDLINE on STN

ACCESSION NUMBER: 2003561148 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14633723
TITLE: Both hepatocyte growth factor (HGF) and stromal-derived factor-1 regulate the metastatic behavior of human rhabdomyosarcoma cells, but only HGF enhances their resistance to radiochemotherapy.
AUTHOR: Jankowski Kacper; Kucia Magda; Wysoczynski Marcin; Reca Ryan; Zhao Dongling; Trzyna Ela; Trent John; Peiper Stephen; Zembala Marek; Ratajczak Janina; Houghton Peter; Janowska-Wieczorek Anna; Ratajczak Mariusz Z
CORPORATE SOURCE: Stem Cell Biology Program, James Graham Brown Cancer Center, University of Louisville, 529 South Jackson Street, Louisville, KY 40202, USA.
CONTRACT NUMBER: 3P0 SE 10122 (NHLBI)
R01 HL 61796-01
SOURCE: Cancer research, (2003 Nov 15) 63 (22) 7926-35.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040210
Entered Medline: 20040209

AB Rhabdomyosarcomas (RMSs) are frequently characterized by bone marrow involvement. Recently, we reported that human RMS cells express the CXC chemokine receptor-4 (CXCR4) and postulated a role for the CXCR4 stromal-derived factor (SDF)-1 axis in the metastasis of RMS cells to bone marrow. Because RMS cells also express the tyrosine **kinase** receptor c-MET, the specific ligand hepatocyte growth factor (HGF) that is secreted in bone marrow and **lymph node** stroma, we hypothesized that the c-MET-HGF axis modulates the metastatic behavior of RMS cells as well. Supporting this concept is our observation that conditioned media harvested from expanded ex vivo human bone marrow fibroblasts chemoattracted RMS cells in an HGF- and SDF-1-dependent manner. Six human alveolar and three embryonal RMS cell lines were examined. We found that although HGF, similar to SDF-1, did not affect the proliferation of RMS cells, it induced in several of them: (a) locomotion; (b) stress fiber formation; (c) chemotaxis; (d) adhesion to human umbilical vein endothelial cells; (e) trans-Matrigel invasion and matrix metalloproteinase secretion; and (f) phosphorylation of mitogen-activated protein **kinase** p42/44 and AKT. Moreover HGF, but not SDF-1, increased the survival of RMS cells exposed to radio- and chemotherapy. We also found that the more aggressive alveolar RMS cells express higher levels of c-MET than embryonal RMS cell lines and "home/seed" better into bone marrow after i.v. injection into immunocompromised **mice**. Because we could not find any activating mutations in the **kinase** region of c-MET or any evidence for HGF autocrine stimulation, we suggest that the increased response of RMS cell lines depends on overexpression of functional c-MET. We conclude that HGF regulates the metastatic behavior of c-MET-positive RMS cells, directing them to the bone marrow and **lymph nodes**. Signaling from the c-MET receptor may also contribute to the resistance of RMS cells to conventional treatment modalities.

L17 ANSWER 8 OF 24 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-00219 BIOTECHDS
TITLE: Suppression of met expression: A possible cancer treatment; potential prostate cancer gene therapy involving use of ribozyme against receptor protein-tyrosine-**kinase**
AUTHOR: SHINOMIYA N; WOUDE GFV
CORPORATE SOURCE: Van Andel Res Inst
LOCATION: Shinomiya N, Van Andel Res Inst, Oncol Mol Lab, 333 Bostwick

NE, Grand Rapids, MI 49503 USA
SOURCE: CLINICAL CANCER RESEARCH; (2003) 9, 14, 5085-5090
ISSN: 1078-0432
DOCUMENT TYPE: Journal
LANGUAGE: English
AB DERWENT ABSTRACT: Met is a receptor protein-tyrosine-**kinase** (EC-2.7.1.112) and the only known receptor for HGF/SF. This ligand/receptor signaling pair mediates a vast range of biological activities not only in normal organ development and physiological functions but also in tumor proliferation, progression, invasion, and metastasis. Tumor cells that express high levels of Met molecules on their surface are more malignant and metastatic. In many carcinomas, HGF/SF acting in a paracrine manner is produced by **stromal cells** adjacent to the tumor. Inhibition of Met expression suppresses the malignant progression of tumor cells. A ribozyme strategy has been used to suppress the growth of human glioblastorna tumors. Because overexpression of Met receptors is observed in a wide spectrum of carcinomas and considered to play a key role in the progression of cancer cells, targeting of this molecule could become one of the most useful treatment modalities for refractory cancers. Molecular targeting of the Met signaling pathways by using specifically designed genes. which target c-met, can be used as a treatment modality for controlling tumor growth and metastasis. An adeno virus vector expressing c-Met ribozyme inhibits tumorigenicity and **lymph node** metastasis of human prostate cancer cells by using an orthotopically implanted in vivo **mouse** model. In prostate cancer cells especially, high expression of Met is associated with resistance against chemotherapy including hormonal therapy and is often observed in the advanced stages of clinical cases. By reducing Met expression using a ribozyme that targets Met mRNA, tumor growth and **lymph node** metastasis were dramatically inhibited(6 pages)

L17 ANSWER 9 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003543598 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12881311
TITLE: Complexity within the plasma cell compartment of **mice** deficient in both E- and P-selectin: implications for plasma cell differentiation.
AUTHOR: Underhill Gregory H; Kolli K Pallav; Kansas Geoffrey S
CORPORATE SOURCE: Department of Microbiology-Immunology, Northwestern Medical School, 303 E Chicago Ave, Chicago, IL 60611, USA.
CONTRACT NUMBER: HL58710 (NHLBI)
SOURCE: Blood, (2003 Dec 1) 102 (12) 4076-83.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031119
Last Updated on STN: 20040115
Entered Medline: 20040114
AB Antibody-secreting plasma cells represent the critical end-stage effector cells of the humoral immune response. Here, we show that several distinct plasma cell subsets are concurrently present in the **lymph nodes**, spleen, and bone marrow of **mice** deficient in both E- and P-selectin. One of these subsets was a B220-negative immunoglobulin g (IgG) plasma cell population expressing low to negative surface levels of syndecan-1. Examination of the chemotactic responsiveness of IgG plasma cell subsets revealed that migration toward **stromal cell**-derived factor 1/CXC ligand 12 (SDF-1/CXCL12) was primarily limited to the B220-lo subset regardless of tissue source. Although B220-negative plasma cells did not migrate efficiently in response to CXCL12 or to other chemokines for which

receptor mRNA was expressed, these cells expressed substantial surface CXC chemokine receptor-4 (CXCR4), and CXCL12 stimulation rapidly induced extracellular signal regulated **kinase** 1 (ERK1)/ERK2 phosphorylation, demonstrating that CXCR4 retained signaling capacity. Therefore, B220-negative plasma cells exhibit a selective uncoupling of chemokine receptor expression and signaling from migration. Taken together, our findings document the presence of significant heterogeneity within the plasma cell compartment, which suggests a complex step-wise scheme of plasma cell differentiation in which the degree of differentiation and tissue location can influence the chemotactic responsiveness of IgG plasma cells.

L17 ANSWER 10 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:153519 BIOSIS
DOCUMENT NUMBER: PREV200400148159
TITLE: Roles of PLC-beta2, -beta3, and PI3K in T-cell migration to SDF 1-alpha.
AUTHOR(S): Bach, Tami L. [Reprint Author]; Chen, Qing-Min [Reprint Author]; Jordan, Martha S.; Wu, Dianqing; Zigmond, Sally H.; Abrams, Charles S. [Reprint Author]
CORPORATE SOURCE: Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 768a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Chemokines bind G-protein coupled receptors and play an essential role in both the immune and inflammatory responses. In T lymphocytes, little is known about the signaling pathways required for chemokine-mediated cell migration. Phospholipase C (PLC) and phosphatidylinositol 3-**kinase** (PI3K) are two distinct signaling molecules that have been proposed as potential candidates in the regulation of this process. Studies with knockout **mice** have demonstrated a critical role for D3-phosphoinositide production by PI3Kgamma in Galphai-coupled receptor-mediated neutrophil chemotaxis. Similar studies have failed to demonstrate a role for IP3 or DAG production by PLCbeta in this neutrophil response. In the current investigation, peripheral T-cells were isolated from the **lymph nodes** of wild type **mice** and **mice** with loss-of-function mutations of either PI3Kgamma, or both of the two dominant lymphocyte PLCbeta isoforms (PLCbeta2 and PLCbeta3). Using a transwell assay, migration of lymphocytes toward SDF-1alpha (37.5 nM) was quantitated after 3 hours, the time point at which migration was maximal for both wild type and knockout T-cells. We found that lymphocytes isolated from wild type **mice** exhibited an eighteen-fold increase in migration with SDF-1alpha stimulation compared to baseline. In contrast, loss of either PLCbeta2beta3 or PI3Kgamma decreased chemokine-stimulated T-cell migration by 68%+-14% ($p<0.005$) and 12+-4% ($p<0.5$), respectively. The impaired sensitivity of the PLCbeta2/beta3-null T-cells occurred over a wide range of agonist, and in contrast to wild type lymphocytes, a large percentage of migration in the PLCbeta2/beta3-null T-cells was due to SDF-induced chemokinesis and not chemotaxis. Chelation of intracellular calcium by BAPTA (30 nM) decreased the chemotactic response of wild type lymphocytes, but pharmacologic inhibition of PKC isoforms by GF109203x (5 muM) or Go 6976 (5 muM) did not impair T-cell migration. Furthermore, SDF-1alpha-induced calcium efflux

was not detected in the PLCbeta2beta3-null lymphocytes. This suggests that the T-cell migration defect seen in the PLCbeta2/beta3-null T-cells may be due to an impaired ability to increase intracellular calcium, while there appears to be little requirement for the stimulation of PKC. We have also found that inhibition of PI3K by either wortmannin (100 nM) or LY294002 (50 muM), decreased SDF-1alpha-induced migration of wild type cells to near baseline, suggesting that PI3K does contribute to T-cell migration, but the PI3Kgamma isoform contributes relatively little to this process. These results show that in vivo phospholipid second messengers generated by PLCbeta and isoforms of PI3K, other than PI3Kgamma, play a critical role in lymphocyte chemotaxis. Our data demonstrate that although PLCbeta-mediated signaling plays no role in neutrophil chemotaxis, it makes a substantial contribution to this process within T lymphocytes.

L17 ANSWER 11 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:451651 BIOSIS
DOCUMENT NUMBER: PREV200300451651
TITLE: Involvement of **stromal cell**-derived factor-1/CXCR4 signaling in **lymph node** metastasis of oral squamous cell carcinoma.
AUTHOR(S): Uchida, Daisuke [Reprint Author]; Begum, Nasima-Mila; Almofti, Ammar; Kawamata, Hitoshi; Nakashiro, Koh-Ichi; Tateishi, Yoshihisa; Hamakawa, Hiroyuki; Yoshida, Hideo; Sato, Mitsunobu
CORPORATE SOURCE: 2nd Dept. Oral and Maxillofacial Surgery, School of Dentistry, Tokushima University, Tokushima, Japan
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 452. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

L17 ANSWER 12 OF 24 MEDLINE on STN

ACCESSION NUMBER: 2003491192 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14567988
TITLE: Possible role of **stromal-cell**-derived factor-1/CXCR4 signaling on **lymph node** metastasis of oral squamous cell carcinoma.
AUTHOR: Uchida Daisuke; Begum Nasima Mila; Almofti Ammar; Nakashiro Koh-ichi; Kawamata Hitoshi; Tateishi Yoshihisa; Hamakawa Hiroyuki; Yoshida Hideo; Sato Mitsunobu
CORPORATE SOURCE: Second Department of Oral and Maxillofacial Surgery, Tokushima University School of Dentistry, 3-18-15 Kuramoto, Tokushima 770-8504, Japan.. daisuke@dent.tokushima-u.ac.jp
SOURCE: Experimental cell research, (2003 Nov 1) 290 (2) 289-302.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031022
Last Updated on STN: 20031219
Entered Medline: 20031202

AB We examined the role of chemokine signaling on the **lymph node** metastasis of oral squamous cell carcinoma (SCC) using

lymph node metastatic (HNt and B88) and nonmetastatic oral SCC cells. Of 13 kinds of chemokine receptors examined, only CXCR4 expression was up-regulated in HNt and B88 cells. CXCR4 ligand, **stromal-cell**-derived factor-1alpha (SDF-1alpha; CXCL12), induced characteristic calcium fluxes and chemotaxis only in CXCR4-expressing cells. CXCR4 expression in metastatic cancer tissue was significantly higher than that in nonmetastatic cancer tissue or normal gingiva. Although SDF-1alpha was undetectable in either oral SCC or normal epithelial cells, submandibular **lymph nodes** expressed the SDF-1alpha protein, mainly in the **stromal cells**, but occasionally in metastatic cancer cells. The conditioned medium from lymphatic **stromal cells** promoted the chemotaxis of B88 cells, which was blocked by the CXCR4 neutralization. SDF-1alpha rapidly activated extracellular signal-regulated **kinase** (ERK)1/2 and Akt/protein **kinase** B (PKB), and their synthetic inhibitors attenuated the chemotaxis by SDF-1alpha. SDF-1alpha also activated Src family **kinases** (SFKs), and its inhibitor PP1 diminished the SDF-1alpha-induced chemotaxis and activation of both ERK1/2 and Akt/PKB. These results indicate that SDF-1/CXCR4 signaling may be involved in the establishment of **lymph node** metastasis in oral SCC via activation of both ERK1/2 and Akt/PKB induced by SFKs.

L17 ANSWER 13 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003003088 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12393730
TITLE: CCR7-mediated physiological lymphocyte homing involves activation of a tyrosine **kinase** pathway.
AUTHOR: Stein Jens V; Soriano Silvia F; M'rini Christine; Nombela-Arrieta Cesar; de Buitrago Gonzalo Gonzalez; Rodriguez-Frade Jose Miguel; Mellado Mario; Girard Jean-Philippe; Martinez-A Carlos
CORPORATE SOURCE: Department of Immunology and Oncology, Centro Nacional de Biotecnologia/Consejo Superior de Investigaciones Cientificas (CSIC), Madrid, Spain.. jstein@cnb.uam.es
SOURCE: Blood, (2003 Jan 1) 101 (1) 38-44.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030103
Last Updated on STN: 20030331
Entered Medline: 20030318

AB Homing of blood-borne lymphocytes to peripheral **lymph nodes** (PLNs) is a multistep process dependent on the sequential engagement of L-selectin, which mediates lymphocyte rolling along the luminal surface of high endothelial venules (HEVs), followed by activation of lymphocyte integrins and transmigration through HEVs. Within lymphoid tissue, B and T lymphocytes then migrate toward specific microenvironments such as B-cell follicles and the paracortex, respectively. The lymphocyte-expressed chemokine receptor CCR7 is playing an important role during this process, as its HEV-presented ligands CCL19 and CCL21 can trigger rapid integrin activation under flow in addition to inducing a chemotactic response, which may participate in transmigration and/or interstitial migration. Here, we report that Tyrphostin (Tyr) AG490, a pharmacological inhibitor of Janus family tyrosine **kinases** (Jaks), blocked the chemotactic response of primary **mouse** lymphocytes to CCL19 and CCL21 in a dose-dependent manner. Furthermore, Tyr AG490 inhibited rapid CCL21-mediated up-regulation of alpha4 and beta2 integrin adhesiveness in static adhesion assays and under physiological flow, whereas adhesion induced by phorbol myristate acetate remained unaltered. Using intravital microscopy of subiliac PLNs in **mice**

, we found that adoptively transferred Tyr AG490-treated lymphocytes adhered significantly less in HEVs compared with control cells, although L-selectin-mediated rolling was similar in both samples. Finally, we observed rapid Jak2 phosphorylation in CCL21-stimulated primary **mouse** lymphocytes. Thus, our study suggests a role for Jak tyrosine **kinases** during CCR7-mediated lymphocyte recirculation.

L17 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:120036 HCAPLUS
DOCUMENT NUMBER: 138:236622
TITLE: RelB in secondary lymphoid organ development: differential regulation by lymphotoxin and tumor necrosis factor signaling pathways
AUTHOR(S): Yilmaz, Z. Buket
CORPORATE SOURCE: Institut fuer Toxikologie und Genetik, Germany
SOURCE: Wissenschaftliche Berichte - Forschungszentrum Karlsruhe (2002), FZKA 6793, i-xv, 1-117
CODEN: WBFKF5; ISSN: 0947-8620
DOCUMENT TYPE: Report
LANGUAGE: English

AB Primary lymphoid organs are the major sites of lymphopoiesis where lymphocytes proliferate and mature into functional but naive cells. Secondary lymphoid organs are sites where these lymphocytes encounter antigens and elicit immune responses. RelB is a member of the Rel/NF-κB family of inducible dimeric transcription factors. RelB is abundantly expressed in secondary lymphoid organs, such as spleen, **lymph nodes**, and Peyer's patches (PP). RelB-deficient **mice** have improper spleen structure and lack organizing centers for PPs, defects that can not be restored by the adoptive transfer of wild-type bone marrow cells. The work presented here revealed a reduction in expression of the homing chemokines B lymphocyte chemoattractant (BLC) and secondary lymphoid organ chemokine (SLC) in RelB-deficient spleen, suggesting a role for RelB in proper expression of chemokines by splenic **stromal cells**. Moreover, interleukin-7 (IL-7)-induced expression of lymphotoxin (LT) in intestinal cells, a crucial step in early PP development, was not impaired in RelB-deficient embryos, suggesting functional hematopoietic inducers and a defect in LTβ receptor (LTβR) expressing stromal responders. Activation of LTβR signaling in fibroblasts resulted in the specific induction of p52-RelB heterodimers, while tumor necrosis factor (TNF) induced classical p50-RelA NF-κB complexes. LTβR-induced RelB nuclear translocation and DNA binding of p52-RelB heterodimers required the degradation of the inhibitory p52 precursor, p100, which was dependent on the IκB **kinase** (IKK) complex subunit IKKα, but not on IKKβ or IKKγ. In contrast to LTβR signaling, TNFR signaling increased p100 and RelB levels both in cytoplasm and nucleus and RelB was bound to p100 in both compartments. Despite the abundant presence of RelB in the nucleus, RelB DNA binding was almost undetectable in TNF treated fibroblasts. Forced expression of p50 and p52 could not rescue the lack of DNA binding. In contrast, RelB DNA binding increased in cells lacking the C-terminus of p100, but not of p105, strongly suggesting that it is the specific inhibitory function of the C-terminal domain of p100, rather than the lack of the heterodimerization partner, which prevents RelB DNA binding in TNF-stimulated fibroblasts. Thus, RelB and p52 in **stromal cells** could function in the proper development of the spleen by regulating the expression of chemokines such as BLC. Furthermore, generation of p52-RelB heterodimers by the LTβR pathway involving p100 degradation, appears to be a critical step in the formation of PP anlage.

REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on

STN

ACCESSION NUMBER: 2003:164949 BIOSIS
DOCUMENT NUMBER: PREV200300164949
TITLE: VEGFR-3 in Cornea Lymphangiogenesis and APC Trafficking.
AUTHOR(S): Chen, L. [Reprint Author]; Hamrah, P. [Reprint Author]; Zhang, Q. [Reprint Author]; Dana, M. R. [Reprint Author]
CORPORATE SOURCE: Department of Ophthalmology, Schepens Eye Research Institute, Harvard Medical School, Boston, MA, USA
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2268. cd-rom. Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 2003
Last Updated on STN: 2 Apr 2003

AB Purpose: Previous data from this lab indicate that lymphatic flow from the cornea to draining **lymph nodes** (LN) plays an important role in corneal immunity. Specifically, corneal transplantation to BALB/c hosts that had their cervical LN excised before surgery showed indefinitely and universal graft acceptance (Yamagami S. & Dana M.R., 2001). VEGFR-3 (Flt-4) is a receptor tyrosine **kinase** which is mainly expressed on the lymphatic endothelium in adult tissues. The purpose of this study is to elucidate the expressional changes of VEGFR-3 during corneal neovascularization (NV) and its possible roles in cornea lymphangiogenesis and APC trafficking. Methods: Corneal NV was induced by intrastromal 11-0 nylon sutures in Balb/c **mice**. Eyes were procured 1, 3, 7, 14 days after the manipulation. Lymphatic vessels and VEGFR-3 positive cells were identified by confocal microscopy with immunofluorescence staining. Results: Cornea lymphatic vessels were detected with VEGFR-3 and CD31 double staining in corneal whole mounts starting at day 3 during induction of corneal NV. Cross sectional studies additionally revealed that the ocular surface epithelium of normal eyes express high levels of VEGFR-3. A sharp increase in VEGFR-3 staining in the corneal stroma was observed during the first week after induction of NV and a transient increase of VEGFR-3 expression on the epithelial layers of the limbus and conjunctival region around day 3 was also found. Additionally, corneal inflammation was associated with enhanced expression of VEGFR-3 by CD11c+ corneal dendritic cells. Conclusion: The expression of VEGFR-3 in the cornea and ocular surface is modified during corneal NV, both at the level of lymphatic vessels, and epithelial and **stromal cells**. These changes may affect trafficking of antigens and/or antigen-presenting cells from the eye to lymphoid organs and provide one explanation for why eyes with NV are considered 'high-risk' candidates for allograft survival. Additional studies including the use of recombinant VEGFR-3 chimeric protein in allograft cornea transplantation were undertaken to further define the possible functional roles of this receptor in lymphatic drainage and graft survival. Support: NIH/NEI Grant EY12963.

L17 ANSWER 16 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:356767 BIOSIS
DOCUMENT NUMBER: PREV200300356767
TITLE: Loss of Function Mutations of PI3Kgamma or PLCbeta2/beta3 Impair T-Cell Migration to SDF.
AUTHOR(S): Bach, Tami L. [Reprint Author]; Huang, Minzhou [Reprint Author]; Wu, Dianqing [Reprint Author]; Zigmond, Sally H. [Reprint Author]; Abrams, Charles S. [Reprint Author]
CORPORATE SOURCE: Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract

No. 2633. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 18 Sep 2003

AB Leukocyte chemotaxis plays a role in both the immune and inflammatory response. **Stromal cell**-derived factor-1alpha (SDF-1alpha) is a member of the CXC chemokine subfamily that stimulates T lymphocytes via activation of a Galphai-coupled receptor. Studies with knockout **mice** have demonstrated a critical role for D3-phosphoinositide production by phosphatidylinositol 3-**kinase** gamma (PI3Kgamma) in Galphai-coupled receptor mediated neutrophil chemotaxis. Similar studies have failed to demonstrate a role for IP3 or DAG production by phospholipase Cbeta (PLCbeta) in this neutrophil response. The role of phospholipid second messengers generated by PI3Kgamma or PLCbeta in lymphocyte chemotaxis is less well known. In the current investigation, **murine** T lymphocytes were studied to determine whether loss of function mutations within either PI3Kgamma, or both of the two dominant lymphocyte PLCbeta isoforms (PLCbeta2 & PLCbeta3), affected lymphocyte migration in response to SDF-1alpha. Using a transwell assay, peripheral T-cells were isolated from the **lymph nodes** of knockout and control **mice**. Migration from the top chamber into the bottom chamber after 3 hours was quantitated in the absence, or presence, of 37.5 nM SDF-1alpha in the lower chamber. Flow cytometry was used to quantitate the number of cells in each chamber. The lymphocytes isolated from control wild type **mice** exhibited a 2.5-4-fold increase in migration with SDF-1alpha stimulation compared to baseline. In contrast, loss of either PI3Kgamma or PLC beta2/beta3 decreased chemokine-stimulated cell migration by 29.0% +/- 5.5% ($p<0.05$) and 49.3% +/- 3.1% ($p<0.001$), respectively. Furthermore, inhibition of PI3K by either wortmannin (233 nM) or LY294002 (50 muM), completely eliminated SDF-1alpha-induced migration of either the wild type cells or cells lacking PI3Kgamma. This latter observation suggests that PI3K isoforms other than PI3Kgamma, also contribute to the chemotactic response. These results show that in vivo phospholipid second messenger formation by both PI3Kgamma and PLCbeta plays a critical role in lymphocyte chemotaxis. Our data demonstrate that although PLCbeta-mediated signaling plays no role in neutrophil chemotaxis, it makes a substantial contribution to this process within T-lymphocytes.

L17 ANSWER 17 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001357671 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11418238
TITLE: Identification of a new fibroblast growth factor receptor, FGFR5.
AUTHOR: Sleeman M; Fraser J; McDonald M; Yuan S; White D; Grandison P; Kumble K; Watson J D; Murison J G
CORPORATE SOURCE: Genesis Research and Development Corporation Ltd., 1 Fox Street, Parnell, Auckland, New Zealand.
SOURCE: Gene, (2001 Jun 27) 271 (2) 171-82.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF321300; GENBANK-AF321301
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827

Last Updated on STN: 20010827
Entered Medline: 20010823

AB A novel fibroblast growth factor receptor (FGFR), designated FGFR5, was identified from an EST database of a **murine lymph node stromal cell** cDNA library. The EST has approximately 32% identity to the extracellular domain of FGFR1-4. Library screening with this EST identified two full-length alternative transcripts which we designated as FGFR5 beta and FGFR5 gamma. The main difference between these transcripts is that FGFR5 beta contains three extracellular Ig domains whereas FGFR5 gamma contains only two. A unique feature of FGFR5 is that it does not contain an intracellular tyrosine **kinase** domain. Predictive structural modelling of the extracellular domain of FGFR5 gamma suggested that it was a member of the I-set subgroup of the Ig-superfamily, consistent with the known FGFRs. Northern analysis of **mouse** and human FGFR5 showed detectable mRNA in a broad range of tissues, including kidney, brain and lung. Genomic sequencing identified four introns but identified no alternative transcripts containing a tyrosine **kinase** domain. Extracellular regions of FGFR5 beta and 5 gamma were cloned in-frame with the Fc fragment of human IgG(1) to generate recombinant non-membrane bound protein. Recombinant FGFR5 beta Fc and R5 gamma Fc demonstrated specific binding to the ligand FGF-2, but not FGF-7 or EGF. However, biological data suggest that FGF-2 binding to these proteins is with lower affinity than its cognate receptor FGFR2C. The above data indicate that this receptor should be considered as the fifth member of the FGFR family.

L17 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:861815 HCAPLUS
DOCUMENT NUMBER: 134:26116
TITLE: Protein and cDNA sequences of human and **mouse** protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor
INVENTOR(S): Bird, Timothy A.; Virca, G. Duke; Martin, Unja; Anderson, Dirk M.
PATENT ASSIGNEE(S): Immunex Corporation, USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073468	A1	20001207	WO 2000-US14696	20000526
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2374612	AA	20001207	CA 2000-2374612	20000526
EP 1181374	A1	20020227	EP 2000-939378	20000526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6514719	B1	20030204	US 2000-579664	20000526
US 2003162277	A1	20030828	US 2003-355975	20030130
US 6759223	B2	20040706		

PRIORITY APPLN. INFO.: US 1999-136781P P 19990528
US 2000-579664 A3 20000526

WO 2000-US14696 W 20000526

AB The invention is directed to purified and isolated novel **murine** and human **kinase** polypeptides, the nucleic acids encoding such polypeptides, processes for production of recombinant forms of such polypeptides, antibodies generated against these polypeptides, fragmented peptides derived from these polypeptides, and the uses of the above. Protein and cDNA sequences of novel human **mouse** protein **kinase** sequence homologs are identified by querying sequence data bases with DNA sequences from **murine** dendritic cell, **murine lymph node stromal cell**, human dendritic cell and human spleen cDNA library, using an algorithm designed to recognize **kinase** subdomains. The invention further relates to methods for identifying novel **kinase** inhibitor.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 19 OF 24 MEDLINE on STN

ACCESSION NUMBER: 1999113739 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9916701

TITLE: Galectin-1 specifically modulates TCR signals to enhance TCR apoptosis but inhibit IL-2 production and proliferation.

AUTHOR: Vespa G N; Lewis L A; Kozak K R; Moran M; Nguyen J T; Baum L G; Miceli M C

CORPORATE SOURCE: Department of Microbiology and Immunology, University of California, Los Angeles, School of Medicine, 90095, USA.

CONTRACT NUMBER: CA-16042 (NCI)
R29 CA65979-01 (NCI)

SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1999 Jan 15) 162 (2) 799-806.
Journal code: 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199902

ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990208

AB Galectin-1 is an endogenous lectin expressed by thymic and **lymph node stromal cells** at sites of Ag presentation and T cell death during normal development. It is known to have immunomodulatory activity in vivo and can induce apoptosis in thymocytes and activated T cells (1-3). Here we demonstrate that galectin-1 stimulation cooperates with TCR engagement to induce apoptosis, but antagonizes TCR-induced IL-2 production and proliferation in a **murine** T cell hybridoma and freshly isolated **mouse** thymocytes, respectively. Although CD4+ CD8+ double positive cells are the primary thymic subpopulation susceptible to galectin-1 treatment alone, concomitant CD3 engagement and galectin-1 stimulation broaden susceptible thymocyte subpopulations to include a subset of each CD4- CD8-, CD4+ CD8+, CD4- CD8+, and CD4+ CD8- subpopulations. Furthermore, CD3 engagement cooperates with suboptimal galectin-1 stimulation to enhance cell death in the CD4+ CD8+ subpopulation. Galectin-1 stimulation is shown to synergize with TCR engagement to dramatically and specifically enhance extracellular signal-regulated **kinase**-2 (ERK-2) activation, though it does not uniformly enhance TCR-induced tyrosine phosphorylation. Unlike TCR-induced IL-2 production, TCR/galectin-1-induced apoptosis is not modulated by the expression of **kinase** inactive or constitutively activated Lck. These data support a role for galectin-1 as a potent modulator of TCR signals and functions and indicate that individual TCR-induced signals can be independently modulated to specifically affect distinct TCR functions.

L17 ANSWER 20 OF 24 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 1998113479 EMBASE
TITLE: Characteristics of the conditioned medium produced by CA-12 **lymph node stromal cells**.
AUTHOR: Lee S.-H.; Lee D.-S.; Seu Y.-B.; Kim J.-G.; Tsuruo T.; Hong S.-D.
CORPORATE SOURCE: S.-D. Hong, Department of Microbiology, Kyungpook National University, Taegu 702-701, Korea, Republic of. leesh@rockvex.rockefeller.edu
SOURCE: Journal of Microbiology and Biotechnology, (1998) 8/1 (74-80).
Refs: 21
ISSN: 1017-7825 CODEN: JOMBES
COUNTRY: Korea, Republic of
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB CS-21 lymphoma cells that preferentially metastasize to **lymph nodes** after s.c. inoculation into BALB/c **mice** were grown in vitro in the presence of CA-12 **stromal cells** isolated from **lymph nodes**. In order to obtain fundamental data on the identification and characterization of the soluble factors produced by CA-12 **stromal cells**, the conditioned medium of CA-12 **stromal cells** that inhibited apoptosis of CS-21 cells was examined. Various analytical treatments revealed that the soluble factors in CA-12 conditioned medium are very sensitive to heat treatment and trypsinization. Moreover CA- 12 conditioned medium has an affinity with heparin but not with Con-A. In addition to these, the activity of CA-12 conditioned medium was blocked by H- 7, a PKC inhibitor, but the conditioned medium could not induce the differentiation of thymocytes. We concluded that CA-12 conditioned medium contains **stromal cell**-derived apoptosis-inhibitory molecules that play an important role in proliferation of CS-21 cells by suppressing cell apoptosis.

L17 ANSWER 21 OF 24 MEDLINE on STN
ACCESSION NUMBER: 97122514 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8968108
TITLE: Induction of fibroblast gelatinase B expression by direct contact with cell lines derived from primary tumor but not from metastases.
AUTHOR: Segain J P; Harb J; Gregoire M; Meflah K; Menanteau J
CORPORATE SOURCE: Unite Institut National de la Sante et de la Recherche Medicale U 419,Institut de Biologie, Centre Hospitalier Universitaire, Nantes, France.
SOURCE: Cancer research, (1996 Dec 1) 56 (23) 5506-12.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 20000303
Entered Medline: 19970124

AB During cancer progression, tumor cells interact with **stromal cells**. As a consequence, matrix metalloproteinases are produced

that contribute to the degradation of the extracellular matrix. This study used coculture systems to investigate fibroblast interaction with three colon cancer cell lines isolated from a single patient. Cells from primary colorectal carcinoma, but not from corresponding liver or **lymph node** metastases, induced gelatinase B expression by fibroblasts of different tissue origin. Remarkably, direct cell-cell contact was required for this induction, which occurred at the pretranslational level (as revealed by Northern blot analysis) and was completely blocked by anti-beta1 integrin monoclonal antibody, but only partially blocked by anti-alpha5 or anti-alpha(v). Induction was also inhibited by cytochalasin D, staurosporine, or dexamethasone, suggesting the need, respectively, for an organized actin cytoskeleton, protein **kinase** C, and AP-1-driven gene transcription. Our data suggest that direct tumor-**stromal cell** contact is one inductive event involved in matrix metalloproteinase expression by **stromal cells**.

L17 ANSWER 22 OF 24 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 95155187 EMBASE
DOCUMENT NUMBER: 1995155187
TITLE: Involvement of CD45 in adhesion and suppression of apoptosis of **mouse** malignant T-lymphoma cells.
AUTHOR: Hanaoka K.; Fujita N.; Lee S.-H.; Seimiya H.; Naito M.; Tsuruo T.
CORPORATE SOURCE: Laboratory of Biomedical Research, Molecular/Cellular Biosciences Inst., University of Tokyo, 1-1-1, Yayoi,Bunkyo-ku, Tokyo 113, United States
SOURCE: Cancer Research, (1995) 55/10 (2186-2190). ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Mouse** malignant T-lymphoma CS-21 cells undergo apoptotic cell death in vitro in the absence of **lymph node** **stromal cells** but escape apoptosis and proliferate when they are attached to CA-12 **stromal cells**. A monoclonal antibody raised against CS-21 cell surface molecules (MCS-5) recognized a M(r) 168,000 protein, inhibited binding of CS-21 cells to CA-12 **stromal cells**, and suppressed apoptosis in CS-21 cells. To identify the M(r) 168,000 protein, we purified it with MCS-5 affinity chromatography and ion exchange chromatography. Partial amino acid sequences of the purified M(r) 168,000 protein were identical to those of CD45, a transmembrane tyrosine phosphatase. The purified protein possessed tyrosine phosphatase activity and was recognized by an anti-CD45 monoclonal antibody. The M(r) 168,000 protein was identified as CD45. To determine the CD45 isoform, we cloned the CD45 gene from the cDNA library of CS-21. Sixteen or 18 clones encoded CD45RO (CD45 lacking exons 4, 5, and 6), and the remainder lacked exons 4, 5, 6, and 7. Like MCS-5, an anti-CD45 monoclonal antibody, also inhibited binding of CS-21 cells to CA-12 cells and suppressed apoptosis in CS-21 cells. Our present results indicate that CD45RO expressed un CS-21 cells mediates adhesion to CA-12 cells and suppression of apoptosis.

L17 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:491699 HCAPLUS
DOCUMENT NUMBER: 122:236647
TITLE: Apoptosis inhibition by anti-Mr 23,000 (Thy-1) monoclonal antibodies without inducing bcl-2 expression
AUTHOR(S): Fujita, Naoya; Naito, Mikihiko; Lee, Sang-Han;

Hanaoka, Kenji; Tsuruo, Takashi
CORPORATE SOURCE: Inst. Molecular Cellular Biosciences, Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Cell Growth & Differentiation (1995), 6(4), 355-62
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Mouse** malignant T-lymphoma CS-21 cells grow in vitro in the presence of CA-12 **stromal cells**, but they undergo apoptotic cell death with DNA fragmentation when cultured alone. Because apoptosis of CS-21 cells was not inhibited by soluble factors secreted from CA-12 **stromal cells**, cell-cell interactions between the two seemed to be important to inhibit apoptosis. The authors found that CS-21 cell adhesion was mediated by Mr 168,000 and Mr 23,000 proteins and that apoptosis-inhibitory signals were transmitted through these proteins. In this study, the authors identified the Mr 23,000 cell adhesion mol. as a glycosylphosphatidylinositol-anchored Thy-1 (CD90) glycoprotein. Crosslinking of Mr 23,000 protein with anti-Mr 23,000 mAb and a second antibody transiently raised the [Ca2+]i and activated calcineurin in CS-21 cells, as has been observed in normal T lymphocytes stimulated by crosslinking anti-Thy-1 mAbs. However, differing from normal T lymphocytes, CS-21 cells could grow either by the transient increase in [Ca2+]i or by the activation of protein **kinase** C. Furthermore, Mr 23,000 protein-mediated cell survival of CS-21 cells was not accompanied by expression of the apoptosis-inhibiting protein bcl-2, although protein **kinase** C-activated cell survival was attended by bcl-2 expression. These results indicate that the Mr 23,000 protein (Thy-1) of CS 21 lymphoma cells functions as a cell adhesion mol. capable of transducing signals of cell survival and growth that are not followed by bcl-2 expression.

L17 ANSWER 24 OF 24 MEDLINE on STN
ACCESSION NUMBER: 95331136 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7607087
TITLE: Developmental expression of the **mouse** c-rel proto-oncogene in hematopoietic organs.
AUTHOR: Carrasco D; Weih F; Bravo R
CORPORATE SOURCE: Department of Molecular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.
SOURCE: Development (Cambridge, England), (1994 Oct) 120 (10) 2991-3004.
Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950828
Last Updated on STN: 20000303
Entered Medline: 19950814

AB We have studied the expression of the c-rel proto-oncogene during **mouse** embryonic development and adult animals using in situ hybridization and immunocytochemical analysis. c-rel transcripts were detected late in development with an expression pattern that parallels the emergence and diversification of hematopoietic cells. In the embryo, c-rel is expressed first in the mesoderm-derived hematopoietic cells of the liver and later also in other hematopoietic tissues such as thymus and spleen. This correlation between c-rel expression and places of hematopoietic infiltration is conserved in the postnatal period, with expression of c-rel mRNA in the medullary region of the thymus and in splenic B cell areas, including the marginal zone and the outer region of the periarterial sheath. High levels of c-rel transcripts were also

detected in the splenic germinal centers, **lymph nodes** and Peyer's patches. Using double immunofluorescence and cell preparations from different embryonic and adult hematopoietic organs, we have defined the pattern and cell types of c-rel expression in different hematopoietic cell lineages and in the **stromal cell** content of the thymus. By using electrophoretic mobility shift assays, we have also correlated c-Rel expression in spleen with kappa B-binding activity in the form of c-Rel/p50 and c-Rel/p52 heterodimers. The timing and pattern of expression of the c-rel proto-oncogene in the different cell lineages suggest that temporally regulated changes in c-Rel expression may be required for vertebrate hematopoiesis.

```
=> d his

     (FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1       1280537 S KINASE?
L2        385991 S LYMPH(A)NODE?
L3         65436 S STROMAL(W)CELL
L4          5129 S L1 AND L2
L5            92 S L3 AND L4
L6            50 DUP REM L5 (42 DUPLICATES REMOVED)
L7             0 S L3(W)L2(W)L1
L8            15 S L1(2W)L2
L9            13 DUP REM L8 (2 DUPLICATES REMOVED)
L10      6902623 S CLON? OR EXPRESS? OR RECOMBINANT
L11           50 S (L6 OR L9) AND L10
L12      3908319 S MURINE OR MOUSE
L13          176 S MLKS##
L14           31 S L12 AND L13
L15           11 DUP REM L14 (20 DUPLICATES REMOVED)
L16           24 S L6 AND L12
L17           24 DUP REM L16 (0 DUPLICATES REMOVED)

=> s l13 and "mlks-2"
L18            0 L13 AND "MLKS-2"

=> d his

     (FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1       1280537 S KINASE?
L2        385991 S LYMPH(A)NODE?
L3         65436 S STROMAL(W)CELL
L4          5129 S L1 AND L2
L5            92 S L3 AND L4
L6            50 DUP REM L5 (42 DUPLICATES REMOVED)
L7             0 S L3(W)L2(W)L1
L8            15 S L1(2W)L2
L9            13 DUP REM L8 (2 DUPLICATES REMOVED)
L10      6902623 S CLON? OR EXPRESS? OR RECOMBINANT
L11           50 S (L6 OR L9) AND L10
L12      3908319 S MURINE OR MOUSE
L13          176 S MLKS##
L14           31 S L12 AND L13
L15           11 DUP REM L14 (20 DUPLICATES REMOVED)
L16           24 S L6 AND L12
L17           24 DUP REM L16 (0 DUPLICATES REMOVED)
L18            0 S L13 AND "MLKS-2"
```

```
Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1652MXM

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS,
NTIS, LIFESCI' AT 14:48:14 ON 03 FEB 2005
FILE 'MEDLINE' ENTERED AT 14:48:14 ON 03 FEB 2005
FILE 'EMBASE' ENTERED AT 14:48:14 ON 03 FEB 2005
COPYRIGHT (C) 2005 Elsevier Inc. All rights reserved.
FILE 'BIOSIS' ENTERED AT 14:48:14 ON 03 FEB 2005
Copyright (c) 2005 The Thomson Corporation.
FILE 'BIOTECHDS' ENTERED AT 14:48:14 ON 03 FEB 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION
FILE 'SCISEARCH' ENTERED AT 14:48:14 ON 03 FEB 2005
Copyright (c) 2005 The Thomson Corporation.
FILE 'HCAPLUS' ENTERED AT 14:48:14 ON 03 FEB 2005
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'NTIS' ENTERED AT 14:48:14 ON 03 FEB 2005
All rights reserved. (2005)
FILE 'LIFESCI' ENTERED AT 14:48:14 ON 03 FEB 2005
COPYRIGHT (C) 2005 Cambridge Scientific Abstracts (CSA)


COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   208.70     210.38

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -18.98     -18.98

=> d his

     (FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1       1280537 S KINASE?
L2        385991 S LYMPH(A)NODE?
L3         65436 S STROMAL(W)CELL
L4          5129 S L1 AND L2
L5            92 S L3 AND L4
L6            50 DUP REM L5 (42 DUPLICATES REMOVED)
L7             0 S L3(W)L2(W)L1
L8            15 S L1(2W)L2
L9            13 DUP REM L8 (2 DUPLICATES REMOVED)
L10      6902623 S CLON? OR EXPRESS? OR RECOMBINANT
L11           50 S (L6 OR L9) AND L10
L12      3908319 S MURINE OR MOUSE
L13          176 S MLKS##
L14           31 S L12 AND L13
L15           11 DUP REM L14 (20 DUPLICATES REMOVED)
L16           24 S L6 AND L12
L17           24 DUP REM L16 (0 DUPLICATES REMOVED)
L18            0 S L13 AND "MLKS-2"
```

```
=> e bird T a/au
E1          299     BIRD T/AU
E2            1     BIRD T */AU
E3          197 --> BIRD T A/AU
E4            5     BIRD T B/AU
E5            2     BIRD T C/AU
E6          892     BIRD T D/AU
E7           21     BIRD T E/AU
E8           68     BIRD T G/AU
E9           42     BIRD T G C/AU
E10           3     BIRD T GEOFFREY/AU
E11          13     BIRD T GEOFFREY C/AU
E12           1     BIRD T GOEFFREY C/AU

=> s e3
L19         197 "BIRD T A"/AU

=> e virca g d/au
E1            3     VIRCA DUKE/AU
E2            1     VIRCA G/AU
E3          131 --> VIRCA G D/AU
E4           47     VIRCA G DUKE/AU
E5            1     VIRCA GEORGE D/AU
E6            1     VIRCA GEORGE DUKE/AU
E7            1     VIRCAR A V/AU
E8            7     VIRCAVA D/AU
E9            1     VIRCAVA D K/AU
E10           2     VIRCAVA DAINA/AU
E11           7     VIRCAVA L/AU
E12          30     VIRCAVS M/AU

=> s e3-e6
L20         180 ("VIRCA G D"/AU OR "VIRCA G DUKE"/AU OR "VIRCA GEORGE D"/AU OR
              "VIRCA GEORGE DUKE"/AU)

=> e martin u/au
E1            3     MARTIN TYLER I/AU
E2            1     MARTIN TYSON EDWARD/AU
E3          752 --> MARTIN U/AU
E4            2     MARTIN U D/AU
E5            2     MARTIN U J/AU
E6           22     MARTIN U O/AU
E7            1     MARTIN U R/AU
E8            1     MARTIN U T/AU
E9            2     MARTIN UBALDO/AU
E10           1     MARTIN UBALDO J/AU
E11           1     MARTIN UBALDO O/AU
E12           8     MARTIN UCAR A/AU

=> s e3
L21         752 "MARTIN U"/AU

=> e anderson d ma/u
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'EMBASE'
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'MEDLINE'
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'BIOSIS'
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'LIFESCI'
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'HCAPLUS'
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'SCISEARCH'
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'BIOTECHDS'
'U' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'NTIS'
The indicated field code is not available for EXPAND in this
file.  To see a list of valid EXPAND field codes, enter HELP
SFIELDS at an arrow prompt (=>).
```

```
=> e anderson d m/au
E1          66     ANDERSON D L T/AU
E2           1     ANDERSON D LONNIE/AU
E3        1925 --> ANDERSON D M/AU
E4           3     ANDERSON D M */AU
E5           1     ANDERSON D M A/AU
E6           1     ANDERSON D M JR/AU
E7           1     ANDERSON D M N/AU
E8         399     ANDERSON D M W/AU
E9           3     ANDERSON D MICHAEL/AU
E10        349     ANDERSON D N/AU
E11          1     ANDERSON D N E/AU
E12          1     ANDERSON D N W/AU

=> s e3
L22       1925 "ANDERSON D M"/AU

=> d his

     (FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005
L1      1280537 S KINASE?
L2       385991 S LYMPH(A)NODE?
L3        65436 S STROMAL(W)CELL
L4         5129 S L1 AND L2
L5           92 S L3 AND L4
L6           50 DUP REM L5 (42 DUPLICATES REMOVED)
L7            0 S L3(W)L2(W)L1
L8           15 S L1(2W)L2
L9           13 DUP REM L8 (2 DUPLICATES REMOVED)
L10     6902623 S CLON? OR EXPRESS? OR RECOMBINANT
L11          50 S (L6 OR L9) AND L10
L12     3908319 S MURINE OR MOUSE
L13         176 S MLKS##
L14          31 S L12 AND L13
L15          11 DUP REM L14 (20 DUPLICATES REMOVED)
L16          24 S L6 AND L12
L17          24 DUP REM L16 (0 DUPLICATES REMOVED)
L18           0 S L13 AND "MLKS-2"
                E BIRD T A/AU
L19         197 S E3
                E VIRCA G D/AU
L20         180 S E3-E6
                E MARTIN U/AU
L21         752 S E3
                E ANDERSON D M/AU
L22        1925 S E3

=> s l19 or l20 or l21 or l22
L23        3018 L19 OR L20 OR L21 OR L22

=> s l13 and l23
L24           0 L13 AND L23

=> s l4 and l23
L25           1 L4 AND L23

=> d all

L25  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2000:861815  HCAPLUS
```

DN 134:26116
ED Entered STN: 08 Dec 2000
TI Protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor
IN Bird, Timothy A.; **Virca, G. Duke**; Martin, Unja; Anderson, Dirk M.
PA Immunex Corporation, USA
SO PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-54
ICS C12N015-11; C12N015-63; C12N009-12; C12N001-21; C12N005-10; C12N015-09; C07K016-40; C12Q001-48
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 1, 7, 13
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000073468	A1	20001207	WO 2000-US14696	20000526
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2374612	AA	20001207	CA 2000-2374612	20000526
EP 1181374	A1	20020227	EP 2000-939378	20000526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6514719	B1	20030204	US 2000-579664	20000526
US 2003162277	A1	20030828	US 2003-355975	20030130
US 6759223	B2	20040706		
PRAI US 1999-136781P	P	19990528		
US 2000-579664	A3	20000526		
WO 2000-US14696	W	20000526		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000073468	ICM	C12N015-54
	ICS	C12N015-11; C12N015-63; C12N009-12; C12N001-21; C12N005-10; C12N015-09; C07K016-40; C12Q001-48
US 2003162277	ECLA	C12N009/12B1B; C12N009/12B1; C12Q001/48; C12Q001/48B

AB The invention is directed to purified and isolated novel murine and human **kinase** polypeptides, the nucleic acids encoding such polypeptides, processes for production of recombinant forms of such polypeptides, antibodies generated against these polypeptides, fragmented peptides derived from these polypeptides, and the uses of the above. Protein and cDNA sequences of novel human mouse protein **kinase** sequence homologs are identified by querying sequence data bases with DNA sequences from murine dendritic cell, murine **lymph node** stromal cell, human dendritic cell and human spleen cDNA library, using an algorithm designed to recognize **kinase** subdomains. The invention further relates to methods for identifying novel **kinase** inhibitor.
ST cDNA sequence human mouse protein **kinase** homolog
IT Blood cell
Bone marrow
Brain
Heart
Kidney

Liver
Lung
Lymph node
Muscle
Ovary
Pancreas
Placenta
Prostate gland
Spleen
Testis
Thymus gland
Tonsil
(LNRK-1 mRNA in; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(LNRK-1, tissue distribution; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT Animal cell
Bacteria (Eubacteria)
Insect (Insecta)
Plant cell
Yeast
(as host; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT Intestine
(colon, LNRK-1 mRNA in; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT Bioassay
(for identifying compds. that inhibiting **kinase** activity; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT Antibodies
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(monoclonal, to protein **kinase** sequence homologs; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT Molecular cloning
Mouse
Protein sequences
cDNA sequences
(protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT Intestine
(small, LNRK-1 mRNA in; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT 9026-43-1P, Protein **kinase**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(MDCK-1, MDCK-2, MDCK-3, MLSK-1, MLSK-2 or LNRK-1; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT 252658-98-3DP, subfragments are claimed 312334-62-6DP, subfragments are claimed 312334-64-8DP, subfragments are claimed 312334-66-0DP, subfragments are claimed 312334-68-2DP, subfragments are claimed 312334-71-7DP, subfragments are claimed 312334-72-8DP, subfragments are claimed
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(amino acid sequence; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT 245319-37-3 312334-63-7 312334-65-9 312334-67-1 312334-69-3 312334-70-6 312334-73-9
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(nucleotide sequence; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT 312343-86-5 312343-87-6
RL: PRP (Properties)
(unclaimed nucleotide sequence; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

IT 312343-88-7 312343-89-8 312343-90-1 312343-91-2 312343-92-3 312343-93-4
RL: PRP (Properties)
(unclaimed protein sequence; protein and cDNA sequences of human and mouse protein **kinase** sequence homologs, and uses thereof in identifying novel **kinase** inhibitor)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anon; GenBank Database no AI469033 1999
(2) Fu, C; J Biol Chem 1999, V274(43), P30729 HCAPLUS
(3) Nci-Cgap; GenBank Database no AA018361 1996
(4) Ohara; GenBank Database no AB011123 1998
(5) Picciotto, M; J Biol Chem 1993, V268(35), P26512 HCAPLUS
(6) Saito; GenBank Database no AB026289 1999
(7) Su, Y; EMBO J 1997, V16(6), P1279 HCAPLUS
(8) Watanabe; FEBS Lett 2000, V469(1), P19
(9) Watanabe; FEBS Lett 2000, V469(1), P19
(10) Yao, Z; J Biol Chem 1999, V274(4), P2118 HCAPLUS

=> d his

(FILE 'HOME' ENTERED AT 14:00:00 ON 03 FEB 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 14:04:41 ON 03 FEB 2005

```
L1      1280537 S KINASE?
L2       385991 S LYMPH(A)NODE?
L3        65436 S STROMAL(W)CELL
L4         5129 S L1 AND L2
L5           92 S L3 AND L4
L6           50 DUP REM L5 (42 DUPLICATES REMOVED)
L7            0 S L3(W)L2(W)L1
L8           15 S L1(2W)L2
L9           13 DUP REM L8 (2 DUPLICATES REMOVED)
L10     6902623 S CLON? OR EXPRESS? OR RECOMBINANT
L11          50 S (L6 OR L9) AND L10
L12     3908319 S MURINE OR MOUSE
L13         176 S MLKS##
L14          31 S L12 AND L13
```

```
L15          11 DUP REM L14 (20 DUPLICATES REMOVED)
L16          24 S L6 AND L12
L17          24 DUP REM L16 (0 DUPLICATES REMOVED)
L18           0 S L13 AND "MLKS-2"
                E BIRD T A/AU
L19         197 S E3
                E VIRCA G D/AU
L20         180 S E3-E6
                E MARTIN U/AU
L21         752 S E3
                E ANDERSON D M/AU
L22        1925 S E3
L23        3018 S L19 OR L20 OR L21 OR L22
L24           0 S L13 AND L23
L25           1 S L4 AND L23
```

	Issue Date	Pages	Document ID	Title
1	20030828	57	US 20030162277 A1	Calcium/calmodulin-dependent kinase
2	20040706	54	US 6759223 B2	Calcium/calmodulin-dependent kinase
3	20030204	54	US 6514719 B1	Methods for identifying compounds that alter kinase activity

	Issue Date	Pages	Document ID	Title
1	20050113	172	US 20050009750 A1	Fibroblast growth factor receptors and methods for their use
2	20040506	29	US 20040087774 A1	TRAF inhibitors
3	20040325	157	US 20040058849 A1	Fibroblast growth factor receptors and methods for their use
4	20040115	158	US 20040010121 A1	7 Human ovarian and ovarian cancer associated proteins
5	20030828	57	US 20030162277 A1	Calcium/calmodulin-dependent kinase
6	20030724	142	US 20030138795 A1	Polynucleotide encoding a novel human growth factor with homology to epidermal growth factor, BGS-8, expressed highly in immune tissue
7	20030710	35	US 20030130230 A1	Novel anti-cancer therapeutic compounds
8	20021121	51	US 20020173635 A1	Secreted expressed sequence tags (sESTs)
9	20020808	133	US 20020106780 A1	Extracellular matrix polynucleotides, polypeptides, and antibodies
10	20020502	13	US 20020052474 A1	Regulators of apoptosis
11	20040706	54	US 6759223 B2	Calcium/calmodulin-dependent kinase
12	20031118	19	US 6649592 B1	Peptide inhibitors of LFA-1/ICAM-1 interaction
13	20031007	23	US 6630447 B2	Peptide inhibitors of LFA-1/ICAM-1 interaction
14	20030204	54	US 6514719 B1	Methods for identifying compounds that alter kinase activity

	Issue Date	Pages	Document ID	Title
15	20010925	28	US 6294348 B1	TRAF inhibitors
16	20010605	12	US 6242569 B1	Regulators of apoptosis
17	20010206	40	US 6184372 B1	Antisense interleukin 10 and methods of use
18	20000516	28	US 6063585 A	TRAF Inhibitors
19	20000509	28	US 6060303 A	TRAF inhibitors
20	19991221	28	US 6004553 A	TRAF inhibitors
21	19980804	28	US 5789550 A	TRAF inhibitors

	Issue Date	Pages	Document ID	Title
1	20050113	172	US 20050009750 A1	Fibroblast growth factor receptors and methods for their use
2	20040506	29	US 20040087774 A1	TRAF inhibitors
3	20040325	157	US 20040058849 A1	Fibroblast growth factor receptors and methods for their use
4	20030828	57	US 20030162277 A1	Calcium/calmodulin-dependent kinase
5	20030724	142	US 20030138795 A1	Polynucleotide encoding a novel human growth factor with homology to epidermal growth factor, BGS-8, expressed highly in immune tissue
6	20030710	35	US 20030130230 A1	Novel anti-cancer therapeutic compounds
7	20020808	133	US 20020106780 A1	Extracellular matrix polynucleotides, polypeptides, and antibodies
8	20020502	13	US 20020052474 A1	Regulators of apoptosis
9	20040706	54	US 6759223 B2	Calcium/calmodulin-dependent kinase
10	20031118	19	US 6649592 B1	Peptide inhibitors of LFA-1/ICAM-1 interaction
11	20031007	23	US 6630447 B2	Peptide inhibitors of LFA-1/ICAM-1 interaction
12	20030204	54	US 6514719 B1	Methods for identifying compounds that alter kinase activity
13	20010925	28	US 6294348 B1	TRAF inhibitors
14	20010605	12	US 6242569 B1	Regulators of apoptosis
15	20010206	40	US 6184372 B1	Antisense interleukin 10 and methods of use

	Issue Date	Pages	Document ID	Title
16	20000516	28	US 6063585 A	TRAF Inhibitors
17	20000509	28	US 6060303 A	TRAF inhibitors
18	19991221	28	US 6004553 A	TRAF inhibitors
19	19980804	28	US 5789550 A	TRAF inhibitors

	Issue Date	Pages	Document ID	Title
1	20030828	57	US 20030162277 A1	Calcium/calmodulin-dependent kinase
2	20040706	54	US 6759223 B2	Calcium/calmodulin-dependent kinase
3	20030204	54	US 6514719 B1	Methods for identifying compounds that alter kinase activity

	Issue Date	Pages	Document ID	Title
1	20041021	66	US 20040208879 A1	Flt4 (VEGFR-3) as a target for tumor imaging and anti-tumor therapy
2	20040812	76	US 20040156826 A1	Treatment of patients with multiple sclerosis based on gene expression changes in central nervous system tissues
3	20040722	63	US 20040142891 A1	Genes involved in immune related responses observed with asthma
4	20040708	96	US 20040133352 A1	Identification, monitoring and treatment of disease and characterization of biological condition using gene expression profiles
5	20040429	33	US 20040082640 A1	Use of cox-2 inhibitors for preventing immunodeficiency
6	20040318	92	US 20040053863 A1	Sensitization of HER-2/neu overexpressing cancer cells to chemotherapy
7	20040226	138	US 20040038346 A1	Novel human protein kinases and uses therefor
8	20040226	259	US 20040038207 A1	Gene expression in bladder tumors
9	20040226	77	US 20040037820 A1	Flt4 (VEGFR-3) as a target for tumor imaging and anti-tumor therapy
10	20040115	484	US 20040009479 A1	Methods and compositions for diagnosing or monitoring auto immune and chronic inflammatory diseases

11	20031218	59	US 20030232037 A1	Genes involved in immune related responses observed with asthma

	Issue Date	Pages	Document ID	Title
12	20031127	96	US 20030219771 A1	Identification, monitoring and treatment of disease and characterization of biological condition using gene expression profiles
13	20031009	34	US 20030192069 A1	Glycerol kinase gene disruptions, compositions and methods related thereto
14	20031002	69	US 20030185820 A1	Protein belonging to the TNF superfamily involved in signal transduction, nucleic acids encoding same, and methods of use thereof
15	20030828	57	US 20030162277 A1	Calcium/calmodulin-dependent kinase
16	20030807	86	US 20030148298 A1	Methods for diagnosing and treating systemic lupus erythematosus disease and compositions thereof
17	20030724	142	US 20030138795 A1	Polynucleotide encoding a novel human growth factor with homology to epidermal growth factor, BGS-8, expressed highly in immune tissue
18	20030612	39	US 20030108937 A1	Methods and compositions for the diagnosis and treatment of cellular proliferation disorders using 20750
19	20030327	41	US 20030059916 A1	IRAK-4: compositions and methods of use
20	20030206	48	US 20030026759 A1	SCREENING AND THERAPY FOR LYMPHATIC DISORDERS INVOLVING THE FLT4 RECEPTOR TYROSINE KINASE (VEGFR-3)

	Issue Date	Pages	Document ID	Title
21	20021031	59	US 20020159970 A1	Protein belonging to the TNF superfamily involved in signal transduction, nucleic acids encoding same, and methods of use thereof
22	20020808	56	US 20020106689 A1	METHODS FOR DIAGNOSING AND TREATING AUTOIMMUNE DISEASE
23	20020321	138	US 20020034780 A1	Novel human protein kinases and uses therefor
24	20041130	69	US 6824777 B1	Flt4 (VEGFR-3) as a target for tumor imaging and anti-tumor therapy
25	20040810	72	US 6773705 B1	Methods for diagnosing and treating autoimmune disease
26	20040720	48	US 6764820 B2	Screening for lymphatic disorders involving the FLT4 receptor tyrosine kinase (VEGFR-3)
27	20040706	54	US 6759223 B2	Calcium/calmodulin-dependent kinase
28	20040127	51	US 6683059 B1	Mini-E1A gene and gene products
29	20040113	18	US 6677313 B1	Method for gene therapy using nucleic acid loaded polymeric microparticles
30	20031125	21	US 6653064 B1	Method for identifying compounds useful in the therapy of bone disorders
31	20031028	133	US 6638721 B2	Human protein kinases and uses therefor
32	20030909	55	US 6617171 B2	Methods for diagnosing and treating autoimmune disease
33	20030527	170	US 6569432 B1	Prostate-specific membrane antigen and uses thereof
34	20030513	61	US 6562347 B1	Chemokine-tumor antigen fusion proteins as cancer vaccines

	Issue Date	Pages	Document ID	Title
35	20030204	54	US 6514719 B1	Methods for identifying compounds that alter kinase activity
36	20020917	79	US 6451571 B1	Thymidine kinase mutants
37	20020528	91	US 6395712 B1	Sensitization of HER-2/neu overexpressing cancer cells to chemotherapy
38	20020430	73	US 6380362 B1	Polynucleotides, polypeptides expressed by the polynucleotides and methods for their use
39	20011218	87	US 6331396 B1	Arrays for identifying agents which mimic or inhibit the activity of interferons
40	20011204	39	US 6326356 B1	Suppression of neu overexpression using a mini-E1A gene
41	20010807	27	US 6271210 B1	Antisense oligonucleotides for mitogen-activated protein kinases as therapy for cancer
42	20010619	17	US 6248720 B1	Method for gene therapy using nucleic acid loaded polymeric microparticles
43	20010306	51	US 6197754 B1	Suppression of tumor growth by a mini-E1A gene
44	20000822	67	US 6107046 A	Antibodies to Flt4, a receptor tyrosine kinase and uses thereof
45	19991228	27	US 6007991 A	Antisense oligonucleotides for mitogen-activated protein kinases as therapy for cancer
46	19991123	50	US 5989860 A	Human isomerase homologs
47	19990302	72	US 5877010 A	Thymidine kinase mutants

	Issue Date	Pages	Document ID	Title
48	19980929	66	US 5814315 A	Methods for the suppression of neu mediated phenotype in tumors
49	19970729	35	US 5652343 A	Method for purification of L-selectin ligands
50	19970701	70	US 5643567 A	Methods for the suppression of neu mediated tumors by adenoviral E1A and SV40 large T antigen
51	19970429	22	US 5625122 A	Mouse having a disrupted lck gene
52	19970408	29	US 5618709 A	Antisense oligonucleotides specific for STK-1 and method for inhibiting expression of the STK-1 protein
53	19960116	35	US 5484891 A	Selectin ligands
54	19940419	37	US 5304640 A	DNA sequence encoding a selectin ligand

	L #	Hits	Search Text
1	L1	200994	murine or mouse
2	L2	702431	clon$3 or express$3 or recombinant
3	L3	3	"MLSK-2"
4	L4	18754	lymph adj nod$2
5	L5	1902	stromal adj cell
6	L6	6080	l1 same l4
7	L7	21	l5 same l6
8	L8	19	l2 same l7
9	L9	346844	BIRD MARTIN VIRCA ANDERSON
10	L10	3705	l6 and l9
11	L11	5	mlsk$2
12	L12	3	l10 and l11
13	L13	54	l6 same kinase$2
14	L14	0	l13 and MLKS$2

	Issue Date	Pages	Document ID	Title
1	20040429	33	US 20040082640 A1	Use of cox-2 inhibitors for preventing immunodeficiency
2	20040318	92	US 20040053863 A1	Sensitization of HER-2/neu overexpressing cancer cells to chemotherapy
3	20040115	484	US 20040009479 A1	Methods and compositions for diagnosing or monitoring auto immune and chronic inflammatory diseases
4	20031009	34	US 20030192069 A1	Glycerol kinase gene disruptions, compositions and methods related thereto
5	20031002	69	US 20030185820 A1	Protein belonging to the TNF superfamily involved in signal transduction, nucleic acids encoding same, and methods of use thereof
6	20030828	57	US 20030162277 A1	Calcium/calmodulin-dependent kinase
7	20030724	142	US 20030138795 A1	Polynucleotide encoding a novel human growth factor with homology to epidermal growth factor, BGS-8, expressed highly in immune tissue
8	20021031	59	US 20020159970 A1	Protein belonging to the TNF superfamily involved in signal transduction, nucleic acids encoding same, and methods of use thereof
9	20020808	56	US 20020106689 A1	METHODS FOR DIAGNOSING AND TREATING AUTOIMMUNE DISEASE
10	20020321	138	US 20020034780 A1	Novel human protein kinases and uses therefor

	Issue Date	Pages	Document ID	Title
11	20041130	69	US 6824777 B1	Flt4 (VEGFR-3) as a target for tumor imaging and anti-tumor therapy
12	20040810	72	US 6773705 B1	Methods for diagnosing and treating autoimmune disease
13	20040706	54	US 6759223 B2	Calcium/calmodulin-dependent kinase
14	20040127	51	US 6683059 B1	Mini-E1A gene and gene products
15	20040113	18	US 6677313 B1	Method for gene therapy using nucleic acid loaded polymeric microparticles
16	20030909	55	US 6617171 B2	Methods for diagnosing and treating autoimmune disease
17	20030527	170	US 6569432 B1	Prostate-specific membrane antigen and uses thereof
18	20030513	61	US 6562347 B1	Chemokine-tumor antigen fusion proteins as cancer vaccines
19	20030204	54	US 6514719 B1	Methods for identifying compounds that alter kinase activity
20	20020917	79	US 6451571 B1	Thymidine kinase mutants
21	20020528	91	US 6395712 B1	Sensitization of HER-2/neu overexpressing cancer cells to chemotherapy
22	20011204	39	US 6326356 B1	Suppression of neu overexpression using a mini-E1A gene
23	20010306	51	US 6197754 B1	Suppression of tumor growth by a mini-E1A gene
24	20000822	67	US 6107046 A	Antibodies to Flt4, a receptor tyrosine kinase and uses thereof
25	19990302	72	US 5877010 A	Thymidine kinase mutants

	Issue Date	Pages	Document ID	Title
26	19980929	66	US 5814315 A	Methods for the suppression of neu mediated phenotype in tumors
27	19970701	70	US 5643567 A	Methods for the suppression of neu mediated tumors by adenoviral E1A and SV40 large T antigen
28	19970408	29	US 5618709 A	Antisense oligonucleotides specific for STK-1 and method for inhibiting expression of the STK-1 protein

	L #	Hits	Search Text
1	L1	200994	murine or mouse
2	L2	702431	clon$3 or express$3 or recombinant
3	L3	3	"MLSK-2"
4	L4	18754	lymph adj nod$2
5	L5	1902	stromal adj cell
6	L6	6080	l1 same l4
7	L7	21	l5 same l6
8	L8	19	l2 same l7
9	L9	346844	BIRD MARTIN VIRCA ANDERSON
10	L10	3705	l6 and l9
11	L11	5	mlsk$2
12	L12	3	l10 and l11
13	L13	54	l6 same kinase$2
14	L14	0	l13 and MLKS$2
15	L15	28	l13 and l9